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THIRTY-FIFTH ANNUAL SESSION—CHICAGO, ILL., APRIL 5-9, 1954

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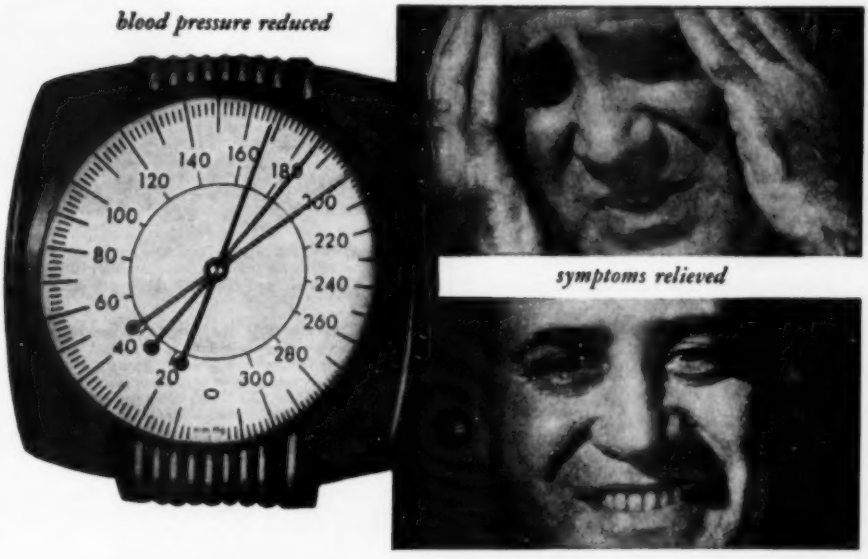

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1. Moyer, J. H., et al.: Am. J. M. Sc. *225*:379 (April) 1953.
2. Mills, L. C., and Moyer, J. H.: A.M.A. Arch. Int. Med. *90*:587 (Nov.) 1952.
3. Frankel, E.: Lancet *1*:408 (Feb. 17) 1951.
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6. Grimson, K. S., et al.: J.A.M.A. *149*:215 (May 17) 1952.
7. Turner, R.: Lancet *1*:1217 (June 2) 1951.

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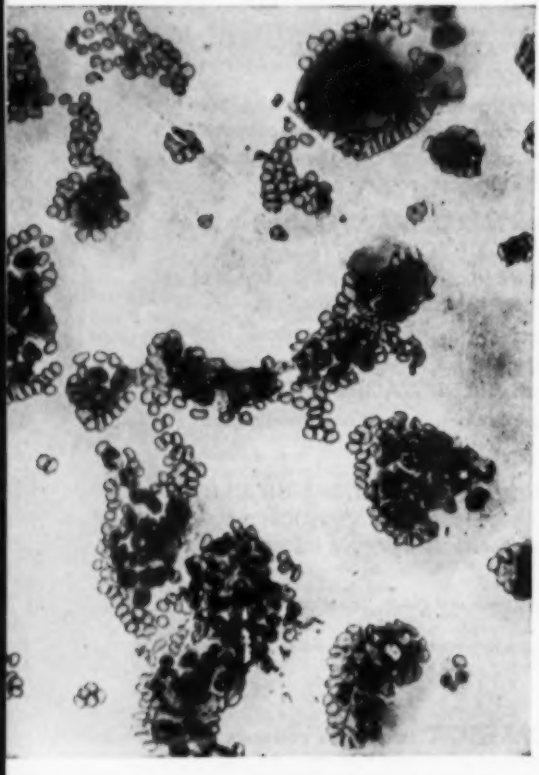

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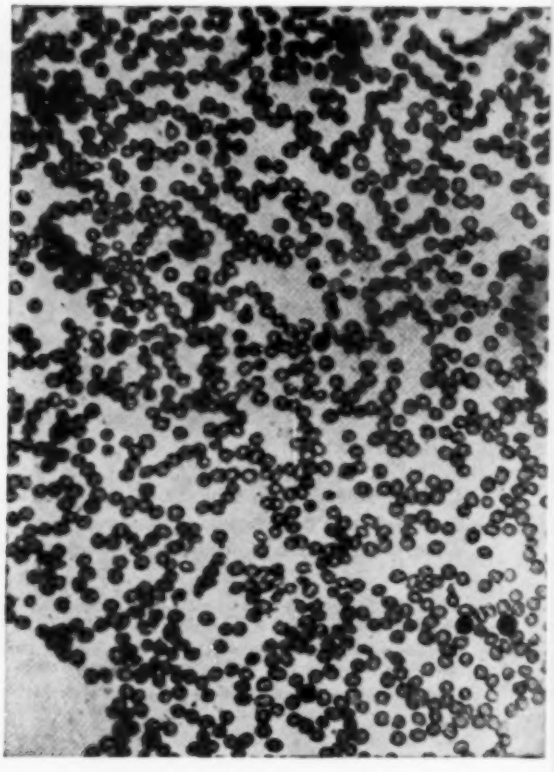

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2. Gardner, Frank H., J. Lab. Clin. Med.; 41:56, 1953.

3. Rohn, R. J. and Bond, Wm. H.; J. Lancet, 73:301, 1953.

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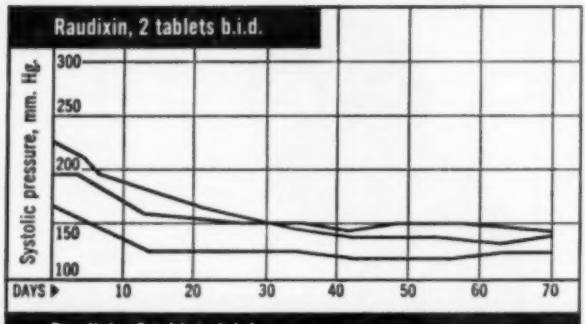

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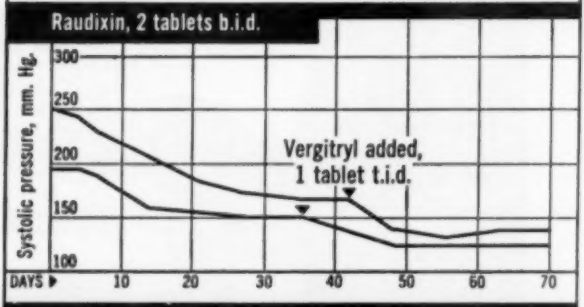

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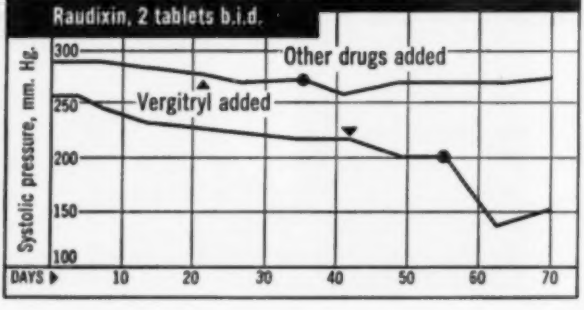

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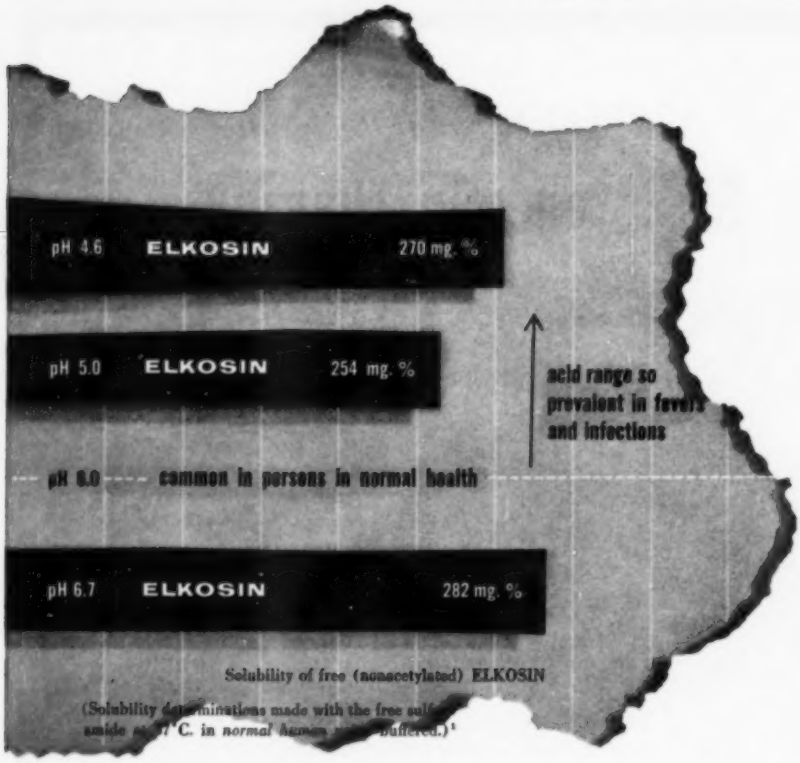

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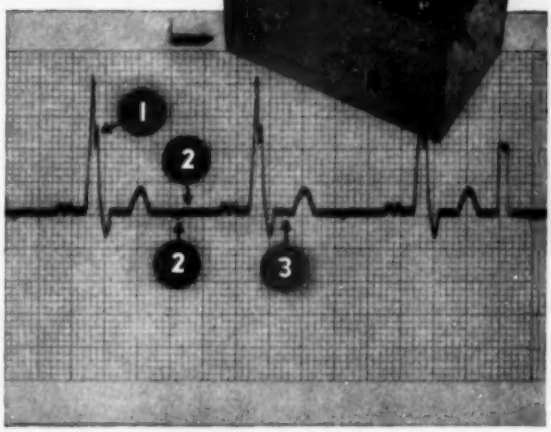

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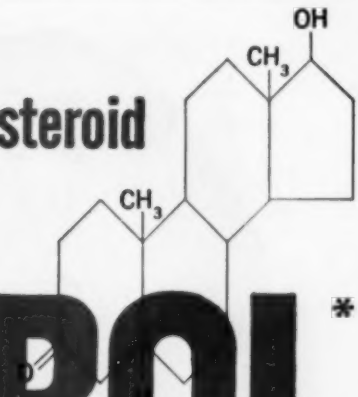

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ANNALS OF
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VOLUME 39 NOVEMBER, 1953 NUMBER 5

CHRONIC SODIUM CHLORIDE TOXICITY: HYPERTENSION, RENAL AND VASCULAR LESIONS *

By GEORGE R. MENEELY, M.D., F.A.C.P., ROBERT G. TUCKER, Ph.D., WILLIAM J. DARBY, M.D., Ph.D., and STEWART H. AUERBACH, M.D., *Nashville, Tennessee*

AN investigation of so common a substance as salt needs an introduction. While used in abundance by nearly all of us every day, we have certainly learned the merit of restricting it in most patients with edema, and there is a growing body of evidence of its rôle in hypertension.[1] A spate of publications on electrolytes in recent years makes one think that nothing before ever was known about salt, and there is some danger of missing the wood for the trees.

Scientific knowledge of the composition of sodium chloride did not exist earlier than 1774, when Scheele first discovered "dephlogisticated marine acid," the greenish yellow gas chlorine. He was confused about it, however, thinking it contained oxygen. In 1807 Davy isolated potassium, the first metal isolated by electricity, and that same year he isolated sodium, also by electrolysis. He named chlorine in 1810. In this, the early part of the nineteenth century, the rise and development of chemical theory was a tumultuous procession. Earlier, Lavoisier had laid the ghost of the phlogiston theory. Besides Davy, Berzelius, Gay-Lussac, Avogadro, Faraday and Liebig were on the stage. The structure and even the electrical nature of salts were understood clearly for the first time by the midpoint of the century. This knowledge replaced the mysteries of the thirteenth century alchemist Geber and the curiously correct speculations of Glauber, he of the salt which is still esteemed as a medicinal in many corners of the globe.[2] By 1850, Carl Schmidt was reporting determinations of sodium and potas-

* Presented at the Thirty-Fourth Annual Session of the American College of Physicians, Atlantic City, New Jersey, April 16, 1953.

From the Research Laboratory and Radioisotope Unit, Thayer Veterans Administration Hospital, and the Departments of Medicine, Biochemistry and Pathology, Vanderbilt University School of Medicine, Nashville, Tennessee.

sium in the blood in his essay on epidemic cholera,[3] and the era of understanding of the physiologic rôle of electrolytes had begun.

These discoveries in the fundamental science of chemistry stimulated a chain reaction among the biologists of that day. Scholars as they were, they looked backward to history as well as forward by observation and experiment. Sodium chloride claimed much attention during the latter half of the nineteenth century in the sphere we have come to call the cultural anthropological, as well as in the fundamental sciences as such.[4]

It is certainly difficult, and perhaps impossible, to trace the earliest human use of common salt. It has been in use by civilized people since earliest recorded history. Evidence from linguistics suggests that salt was not known as such when the stem language developed. There is thought to be no common Indo-European root for the word. Evidence has been assembled [5, 6] which suggests that salt came into use at the time man made the transition from a nomadic hunter-fisher, on a roasted meat and milk diet to an agriculturist on a cereal grain and vegetable diet. The fact that herbivorous animals manifest a craving for salt by travel for long distances to salt licks, while carnivorous animals do not, intrigued the physiologic chemists of the latter half of the nineteenth century. Bunge [7] may have been the first to advance the concept that the high potassium content of a grain and vegetable diet required in the herbivora an increased sodium intake. "Herbivorous animals take at least three or four times as much of the salts of potassium as the carnivorous. This fact leads me to imagine that the abundance of potassium in vegetable food is the cause of the need of salt in the herbivora." [8] Whether this is the true reason agricultural man began adding salt to his diet, certainly once he had he took a great fancy to it. The preservative effect of salt must have been noted early, and food so preserved became vital through the non-harvest seasons and during voyages and migrations. There are many references to salt in the Bible, and there is a rich and entertaining literature concerned with the history, symbolism and financial problems of salt.[9, 10, 11] Lack of salt has been propounded as a major factor in the fall of the Confederacy.[12]

In spite of the popularity of salt, some have surmised that the popular consumption of it was excessive. Jonathan Swift felt it was "an effect of luxury," Crusoe's man Friday despised it, the explorer Stefansson found he did not need it, and Bunge, who from his experimental work had reason to know, said, "We are accustomed to take far too much salt with our viands. Salt is not only an aliment, it is also a condiment and easily lends itself, as all such things do, to abuse." [13]

Two years ago the thought occurred to us that sodium chloride consumption in excess of the amount required for normal nutrition might be a factor in degenerative disease. A search of the literature reveals surprisingly little information about the chronic effects of excess sodium chloride ingestion. Chapman [1] has traced the history of our understanding

TABLE I

Composition of Diets

Basic Ration		Sodium Chloride to Make	
		I (Low NaCl)	0.01%
Cane Sugar	51.9%	II (Control)	0.15%
Casein, Vitamin-test	25.0%	III	2.8 %
Shortening, All-vegetable	20.0%	IV	5.6 %
Mineral Mixture	2.9%	V	7.0 %
Vitamins	0.2%	VI	8.4 %
		VII	9.8 %

of the rôle of sodium chloride in disease. Carrion and Hallion in 1899 produced pulmonary and peripheral edema with salt solutions. Widal and Lemierre in 1903 showed that the edema of Bright's disease was increased by giving salt. Ambard and Beaujard in 1904 were the first to observe a decline in blood pressure following salt restriction in hypertensive patients, but, like others later, they thought that the chloride rather than the sodium was the important factor. Sixteen years later, Allen found a low salt diet effective in the treatment of some patients with hypertension. Kempner [14] in 1944 reported his now well known low-sodium rice-fruit diet. Others have reported on injury due to increased dietary sodium chloride in lower animals, especially fowl, which have a primitive glomerulus, more readily susceptible to injury than that of the mammalia.[15]

Most of the reports on experimental animals included sodium chloride variations and something else, such as steroid medication, parabiosis, fluid restriction, et cetera. The few investigations on salt alone were usually short in duration, with relatively small numbers of animals. Therefore, a long-term experiment was initiated using the male albino rat. The growth and development of these rats have been reported elsewhere,[15] and a detailed

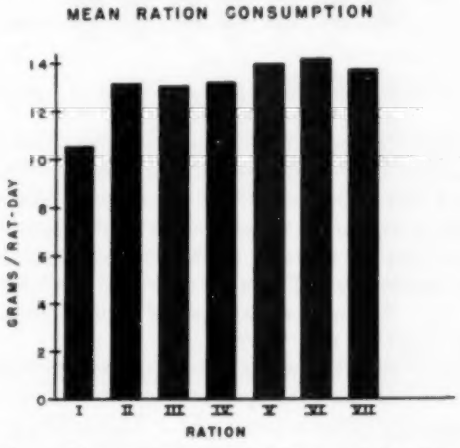

FIG. 1. Mean ration consumption for first five weeks of experiment.

report of other observations is in preparation for publication.[16] It is the purpose here to review in a general way the findings to date.

A basic purified diet was prepared containing all known nutrients in the amounts considered optimal for rats but with as little sodium chloride as possible without going to extremes. This diet by analysis contained 0.01 per cent sodium chloride by weight, perhaps twice an amount so low as to cause failure of growth, decline and death. To this basic ration finely powdered sodium chloride was added to produce six additional rations (table 1). Ration number II, the control diet, contained 0.15 per cent sodium chloride, the amount commonly used in nutritional experiments. The remaining five diets contained 20, 40, 50, 60 and 70 times this amount (2.8 per cent, 5.6 per cent, 7.0 per cent, 8.4 per cent and 9.8 per cent of

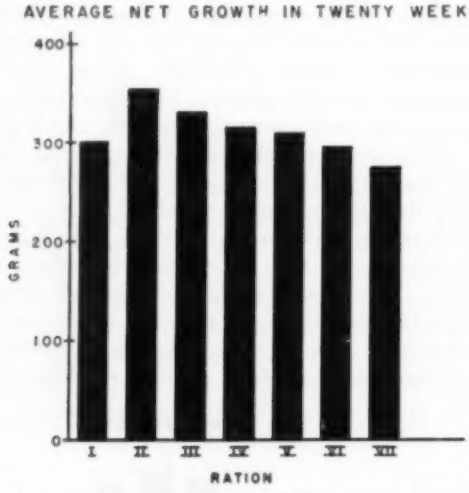

FIG. 2. Average net growth in first 20 weeks of experiment.

NaCl). Thirty male Sprague-Dawley rats were placed on each of the diets except the low-sodium diet, which group was smaller. They were housed in suspended steel wire cages at 27° C. Somewhat surprisingly, after a few days the rats were eating these rations with apparent relish almost without exception, and by the end of the second week they seemed well adjusted, healthy and happy. Those on restricted salt (Ration I) had less appetite (figure 1). The animals all gained weight, but none so well as the control group (figure 2).

Demineralized or distilled water was provided ad libitum. The rats on the higher rations of salt developed and maintained an impressive polyuria and a consequent polydipsia (figure 3). This is not a new observation. Lord Somerville [17] remarked upon increased thirst in cattle given salted

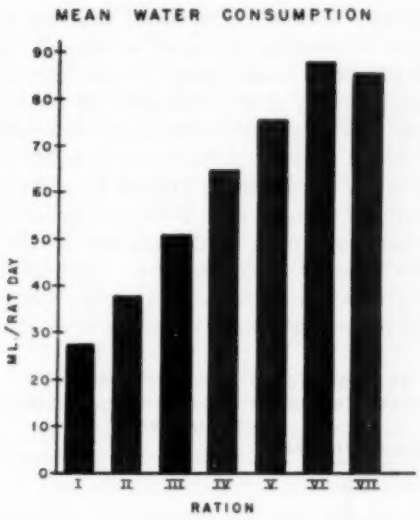

FIG. 3. Mean water consumption for first five weeks of experiment.

hay in an address to the Board of Agriculture in 1814, and it was doubtless well known long before that.

Beginning after two months and continuing thereafter for several months, episodes of massive edema began to occur among the animals eating the three highest rations of salt, that is, from 7.0 to 9.8 per cent. A total of 18 per cent of the 90 rats on these rations were so affected. In such animals, after a period of apparently normal growth an abrupt increase in weight occurred. In some animals the volume of extracellular water estimated with the radioactive isotope of sodium increased to more than twice the normal. Most of the animals who became edematous died or were sacrificed for study. A few passed through the edema phase to a dry cachectic state terminating in emaciation and death.

The clinical syndrome (table 2) exhibited by these edematous animals bore a striking resemblance to the syndrome of nephrosis seen in humans. (We particularly wish to emphasize that this is merely a resemblance. At this time the data are not nearly complete enough to reach a firm conclusion.) Besides the edema, the blood pressure was found to be elevated in most animals in which it was measured. There was a profound anemia.

TABLE II

Clinical Features of a Syndrome Occurring in 18 Per Cent of Rats Eating from 7.0 Per Cent to 9.8 Per Cent NaCl in the Diet at 27°C.

Edema	Lipemia
Hypertension	Hypoproteinemia
Anemia	Azotemia

The plasma was grossly lipemic. The blood proteins were low, and the animals were in a state of nitrogen retention, presumably due to renal failure.

Aside from the relatively small group of rats which developed edema and renal failure, the majority of the remainder of the colony continued in apparent good health, with only the attrition to be expected from intercurrent infection. Reliable blood pressure measurements on the entire colony were obtained beginning in the ninth month (figure 4). As early as this there were frankly hypertensive animals, even in the group on the lowest increased salt diet (2.8 per cent), and most of the animals on the highest ration of salt had striking elevations of blood pressure. Statistical analysis of these data shows that all groups above the control group, that is, groups III, IV, V, VI and VII, had highly significant increases in arterial blood pressures.

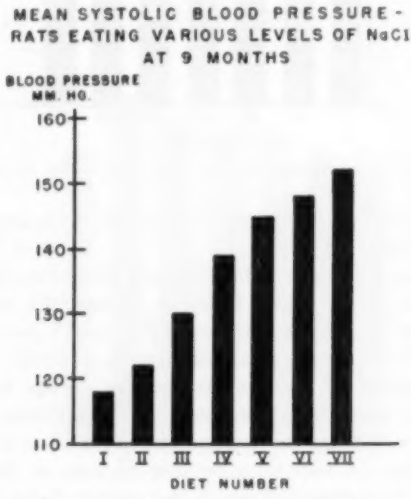

FIG. 4. Mean systolic blood pressure at nine months.

Moreover, the relationship of the blood pressure to the amount of salt in the diet was linear.

Most of these rats are still alive. Hypertension persists among the high salt groups and is increasing. Now, from time to time, instances of renal failure of a somewhat more chronic and slowly developing nature than that previously described are being encountered. In addition, a few animals have developed a syndrome characterized by dyspnea, moderate edema, cardiac enlargement and elevated venous pressure. Seemingly, this represents congestive heart failure. A few of the rats with hypertension have been subject to epistaxis and convulsions.

Some animals from groups III and IV have been sacrificed, although to date there have been no clinical manifestations attributable to hyperten-

sion among them despite the significant elevations of blood pressure. Examination by ordinary methods of the tissues of these rats, including the kidneys and adrenals, does not reveal any microscopic anatomic alterations not seen among control animals similarly sacrificed.

There are important pathologic changes among the animals eating the three highest levels of salt (V, VI and VII). The ground plan of these changes seems similar, whatever the clinical picture the animal may have exhibited. The important differences are in degree and extent of the changes, dependent presumably upon the time of onset of the change, its severity and its distribution. The earliest lesion is seen in the glomerulus, which is relatively bloodless, increased in size, degenerated and containing foam cells which on Sudan IV staining are seen to contain lipid. A more severe stage involves further glomerular deterioration and involvement of the tubules in a devastating degenerative process. The arterioles are involved early, and in advanced stages of the lesion may be seen to have undergone changes resembling those in human malignant hypertension. In such cases, arteriolosclerosis is widespread through the other organs and tissues examined. The adrenals have not revealed structural changes not seen in the control rats. In animals on high salt diets, sacrificed while in apparent good health despite hypertension, the nature of the lesion is the same but is less in degree, and the renal lesion is spotty in distribution, some nephrons apparently escaping entirely while others are severely involved.

We must be cautious in our conclusions from these data. We have demonstrated that increases in salt in the diet of the male rat produce physiologic and pathologic changes which are proportional to the amount of the increase. It is probable that as time goes on rats in groups III and IV which do not reveal microscopic anatomic changes as yet will begin to show such changes, because most of these animals have sustained hypertension. The parallel to human hypertension is of course obvious, but nothing we have shown here can be directly applied to the human without extensive further study to evaluate the sensitivity of humans to salt. Nevertheless, we can hardly fail to mention that diet III (2.8 per cent NaCl) compares roughly on a weight-for-nutrient basis with a human intake of about 12 gm. of salt per day, a value which is often regarded as the national average.

Summary

In view of the paucity of information relative to the chronic effects of sodium chloride in the diet of mammalia, a long-term study has been undertaken in the male albino rat. Purified rations, containing from 0.01 per cent to 9.8 per cent of NaCl, and water were fed at will from the age of five weeks. Diets both high and low in sodium chloride reduced the rate of growth. Water consumption was related directly to the amount of salt in the diet. A low-sodium diet depressed the appetite, but diets high in sodium chloride did not. Edema developed in 18 per cent of the rats eating

the diets which contained from 7.0 per cent to 9.8 per cent of NaCl. Pathologic lesions were observed in the kidneys and to a lesser extent in various other tissues of rats consuming these high levels of salt. Sustained arterial hypertension was observed in the rats eating high levels of sodium chloride after nine months of the dietary regimen. A linear relationship was found to exist between the NaCl concentration in the diet and the systolic blood pressure.

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THE TREATMENT OF HYPERTENSION WITH DRUGS *

By MILTON MENDLOWITZ, M.D., F.A.C.P., *New York, N. Y.*

THERE are times when the strident conflicts of investigators, the rise and fall of theories and the babel of unsorted evidence create such a sense of confusion in a field that an atmosphere of frustration and despair prevails in which no one believes anything; this has happened to some extent in hypertension.[1, 2] Yet somewhere between the extreme skepticism both of the very young and of the old and tired, and the transient enthusiasms of the protagonists of this theory or that remedy, lies a middle ground of achievement and even agreement. It is generally agreed, for example, that the cause of ordinary hypertension is narrowing of the terminal vascular bed of the systemic circulation, especially the arterioles.[3, 4] It is also generally believed, although with some dissension, that there are three major causes of such narrowing.[5, 6, 7] One is increased discharge via the sympathetic nervous system. Another is increased vasomotor tone produced either by circulating substances or by metabolic changes. A final cause is structural changes in the vessels themselves, frequently influenced at least in part by the first two factors.

What is more, in the ordinary hypertensive the neurogenic factor is usually the first and, as believed by some, the initiating factor in the process. The humoral or metabolic element contributes later, when the kidney participates in the disease. This factor accelerates the disease by increasing vasomotor tone, and, finally, the structural changes in the arterioles produced in part by these influences turn the screw tighter.

The greatest area of conflict has been the nature of the humoral or metabolic factor, and even this area has been narrowed.[2] There was a body of thought at one time holding circulating epinephrine or nor-epinephrine responsible at least in part for hypertension, but except in the unusual cases of chromaffin tumors it is now accepted that these hormones play insignificant rôles in the pathogenesis of hypertension.[8] Many workers still believe that the kidney secretes a "pressor" substance,[2, 9] whereas others attribute the defect to some alteration in salt and water metabolism produced by the diseased kidney,[10] and here adrenal cortical hormones probably also influence the final balance.[11, 12]

In recent years another theoretic possibility has been suggested, namely, that hypertension consists of increased reactivity on the part of the vasomotor complex to ordinary stimuli, both nervous and humoral or metabolic.[13] The

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From the Department of Medicine, The Mount Sinai Hospital, New York, N. Y.
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TABLE I

Blocking Drugs

Drugs	Site of Action	Block	Mode of Administration	Dosage	Duration of Effect	Major Side Actions	Tolerance
1. Procaine	Sensory and moderator nerves	Sympathetic + Parasympathetic +	i.v.	Variable		Collapse	
2. Barbiturates Rauwolfia serpentina Bromides, other hypnotics, narcotics anesthetics	Cerebral cortex	Sympathetic ++ Parasympathetic ±	p.o. p.h. i.v. Inhalation	Variable		Somnolence, respiratory depression	++
3. Veratrum alkaloids (Protoveratrine) (Veroxin)	Hypothalamus	Sympathetic ++ Parasympathetic ±	p.o. i.v. i.m.	1–3 mg. t.i.d. 1–3 mg.	Moderate	Nausea, vomiting, cardiotoxic?	+
4. 1-hydrazinophthalazine	Hypothalamus	Sympathetic +++ Parasympathetic ±	p.o.	50–200 mg. q. 4 h.	Moderate	Leg edema. Postural hypotension. Nausea, vomiting, drug fever, psychosis. Headache, nasal congestion	+
5. Hydrogenated ergot derivatives (Hydergine)	Hypothalamus	Sympathetic +++ Parasympathetic 0	i.v. i.m. s.l.	0.3 mg. 0.3 mg. b.i.d. 0.3 mg. t.i.d.	Moderate	Postural hypotension, nasal congestion, nausea. Smooth muscle spasm?	+
6. Procaine	Spinal cord	Sympathetic +++ Parasympathetic +	i.s.			Collapse	
7. Tetraethylammonium salts (TEAC)	Autonomic ganglia	Sympathetic +++ Parasympathetic +	i.v. i.m.	5 mg./kg. 10 mg./kg.	Short	Tingling, paralysis of accommodation, postural hypotension, nausea, vomiting, shock	
8. Quaternary amines (SC–1950)	Autonomic ganglia	Sympathetic +++ Parasympathetic ±	i.v. i.m.	5–50 mg. 5–50 mg. b.i.d.	Moderate	As above except for tingling	
9. Penta- and hexamethonium salts	Autonomic ganglia	Sympathetic ++++ Parasympathetic ±	i.v. i.m. p.h. p.o.	5–50 mg. 5–50 mg. b.i.d. 250–1,000 mg. q. 4 h.	Long	As above, relative bradycardia, postural hypotension and collapse. Bromism if bromide salt is used. Oral preparation causes constipation and may cause paralytic ileus.	

TABLE I—*Continued*

Drugs	Site of Action	Block	Mode of Administration	Dosage	Duration of Effect	Major Side Actions	Tolerance
10. Methantheline bromide (Banthine)	Autonomic ganglia Autonomic nerve endings	Sympathetic + Parasympathetic +++	p.o.	50–100 mg. q. 6 h.	Moderate	Nausea, vomiting, bladder paralysis.	
11. Dibenamine	Autonomic nerve endings	Sympathetic ++ Parasympathetic 0 Circulating epinephrine and nor-epinephrine ++	p.o. i.v.	5 mg./kg. t.i.d. 4–6 mg./kg.	Moderate	Postural hypotension, nasal congestion, nausea, vomiting	++
12. Dibenzyline (SKF 688A)	Autonomic nerve endings	Sympathetic ++ Parasympathetic + Circulating epinephrine and nor-epinephrine ++	p.o.	20–60 mg. t.i.d.	Moderate	Postural hypotension, nasal congestion, nausea, vomiting	++
13. V D M (Ferritin)	Autonomic nerve endings	Sympathetic + Parasympathetic 0 Epinephrine +					
14. Piperoxan (Benzodioxane)	Autonomic nerve endings	Sympathetic ± Parasympathetic 0 Epinephrine ++ Nor-epinephrine ++	i.v.	10 mg./sq. m.	Short	Hypertension and tachycardia	
15. 2((m-hydroxy-N-p-tolylanilino)-methyl)-2-imidazoline (Regitine)	Autonomic nerve endings	Sympathetic + Parasympathetic 0 Epinephrine ++ Nor-epinephrine ++	i.v. i.m.	5 mg.	Short		
16. Atropine group	Basal ganglia, autonomic nerve endings	Sympathetic 0 Parasympathetic +++	i.m. p.h. p.o.	Variable	Moderate	Dry mouth, mydriasis, excitability	
17. Nitrites	Smooth muscle of arterioles	Sympathetic ± Parasympathetic ± Smooth muscle ++	p.o. Inhalation s.l. p.h.	60 mg. (sod. nitrite) t.i.d. Amyl nitrite Perles. Nitroglycerin 0.6 mg.	Moderate	Headache, collapse	

TABLE I—*Continued*

Drugs	Site of Action	Block	Mode of Administration	Dosage	Duration of Effect	Major Side Actions	Tolerance
18. Xanthine group (Theophyllin, Aminophyllin)	Smooth muscle of arterioles, capillaries, salt and water balance (diuresis)	Sympathetic ± Parasympathetic ± Smooth muscle + Capillaries +	p.o. i.v. Suppos.	0.2–0.4 gr. t.i.d. 0.25 gm. 0.5 gm.	Moderate	Collapse (rarely)	
19. Adenosine triphosphate	Smooth muscle of arterioles, heart	Sympathetic 0 Parasympathetic 0 Smooth muscle ++	i.m. i.v.		Short	Cardiotoxic?	
20. 2-benzyl imidazoline hydrochloride (Priscoline)	Autonomic nerve endings and capillaries	Sympathetic + Parasympathetic 0 Capillaries +++	i.a. i.v. p.o.	25–50 mg. 50 mg. 25–50 mg. q. 4 h.	Moderate	Tingling, erythema, nausea	
21. Histamine	Capillaries	Sympathetic ± Parasympathetic ± Capillaries ++++	i.v. p.h. i.a.	0.05 mg. 0.1 mg. 0.05 mg.	Short	Headache, shock, gastric hyperacidity	
22. Thiocyanates	Capillaries? Salt and water balance? Oxidative enzymes	Sympathetic ± Parasympathetic ± Capillaries + Indirect	p.o.	0.3 mg. t.i.d. (Blood level should not exceed 12 mg. %)	Moderate	Agranulocytosis, glossitis, gingivitis, encephalitis	
23. Mercurial diuretics Exchange resins	{Capillaries, Water and salt balance—Kidney}	Indirect	i.m. i.v. p.h.	1–2 c.c.	Long	Low salt syndrome, shock, mercurial intoxication (rare)	
24. Digitalis group	Hypothalamus. Heart. Smooth muscle of venules and arterioles. {Kidney (diuresis) Capillaries. Water and salt balance}	Sympathetic ± Parasympathetic ± Smooth muscle + Capillaries + Indirect	p.o. i.v.	Variable	Long	Arrhythmias, nausea, vomiting, somnolence	

evidence for this is usually based on the "pressor" response to epinephrine, or nor-epinephrine, a most complex phenomenon involving the central nervous system, the heart and the sympathetic nervous system. There is evidence that adrenal cortical hormones affect reactivity in this loose sense,[14, 15] but it is not known whether the action is on the nervous system, the heart or directly on the blood vessels.

Most therapy in the disease is directed at the neurogenic factor, although the failure of sympathectomy to influence the disease favorably in many cases has discouraged this attack.[16] However, a closer examination of the effects of this operation should be reassuring.[17] Most sympathectomies are incomplete, and compensatory vasoconstriction develops in the intact regions which tends to counteract the effect of the operation. Also, ganglion cell nests in the anterior nerve roots often take over the burden of sympathetic outflow, even in areas comparatively denervated by the sympathectomy. In addition, the intrinsic resistance of sympathectomized vessels often increases, perhaps because of atrophy of disuse and shortening of the smooth muscle of the arterioles. For all these reasons sympathectomy is often unsuccessful, but not because decrease in sympathetic nerve discharge is undesirable in hypertension. Therefore, most drugs which are aimed at decreasing sympathetic nerve discharge are successful to some extent in hypertension (table 1). The important limitations are those of side effects and tolerance.

To understand the action of these drugs it is important to review the anatomic features of the elaborate system of relays ending in the final common pathway of the sympathetic nervous system (figure 1).[18] Sensory inflow to this system can come from anywhere in the body via way stations in the spinal ganglia, the brain stem, cerebellum, thalamus, and the cerebral cortex itself. Very important sensory regulatory impulses come to the medulla via the carotid sinus and aortic nerves.[19] These inhibit outflow, especially from the hypothalamus. On the motor side there are four separate synapse levels: (1) in the cerebral cortex, (2) in the hypothalamus, (3) in the spinal cord, and (4) in the sympathetic ganglia. Blocking drugs may act at any one of these levels or on the nerve endings. There are also drugs which interrupt sensory inflow, whereas others have a direct blocking action on the contractility of smooth muscle or of capillaries. Some drugs also have indirect actions which influence either reactivity of the blood vessels to ordinary stimuli, or the non-neurogenic or intrinsic tone of these vessels.

Theoretically, any drug which effectively blocks sensory inflow to this system could diminish sympathetic nerve discharge and decrease vasomotor tone. This may be neutralized in part by blocking the moderator nerves, which are ordinarily inhibitory. Intravenous procaine is such a drug, but in ordinary dosage it has very little effect on the blood pressure or on vasomotor tone.[20, 21] Larger doses which might inhibit sympathetic nerve discharge are interdicted by undesirable side actions.

Hence most drugs are aimed at the various synapse levels on the motor

side of the relay system. There are many substances which block sympathetic outflow at the level of the cerebral cortex, including alcohol, the anesthetics, the narcotics and the hypnotics. Phenobarbital is still the drug most widely used for hypertension. It acts by blocking asympathetic out-

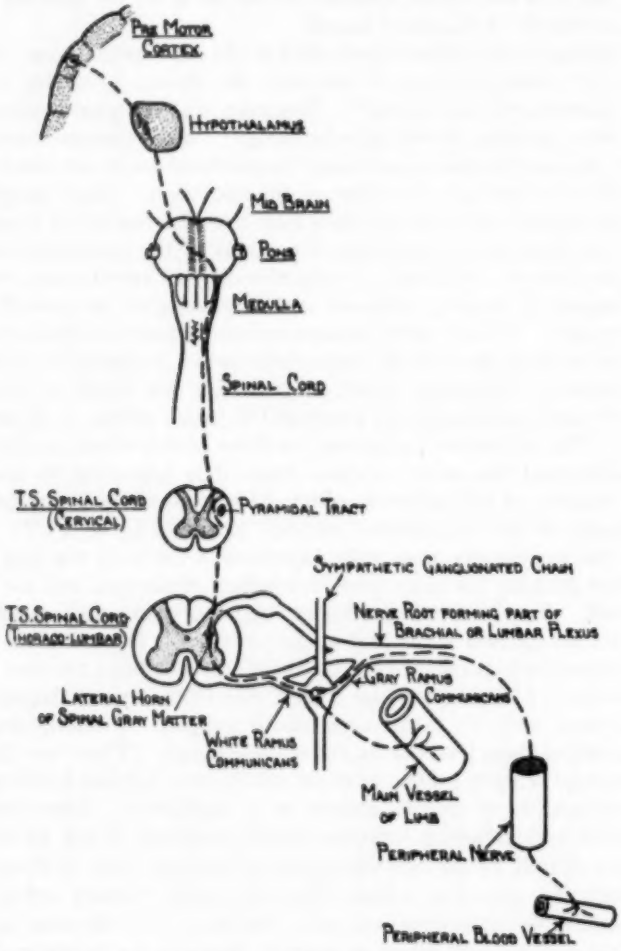

FIG. 1. Diagram of motor synapses controlling sympathetic vasomotor tone (Richards [18]).

flow at the cortical level.[21, 22] A newer drug, acting probably on cortical and subcortical centers, is Rauwolfia serpentina.[23] When these drugs are given in quantities sufficient to produce complete inhibition of sympathetic nerve discharge, side effects frequently limit their usefulness. The major

undesirable side action of phenobarbital is somnolence. Tolerance may also limit the use of these preparations.

Acting at the hypothalamic level are a group of compounds recently the subject of considerable attention. These include the veratrum alkaloids, hydrogenated ergot derivatives and 1-hydrazino-phthalazine. Veratrum alkaloids [24, 25, 26] are available in mixtures such as Veriloid and veratrum viride, and as purified products such as veroxin and protoveratrine.[27] Nausea and vomiting are common side actions which limit the prolonged use of these compounds, although this is less often observed with the purer drugs. There is still some doubt as to whether all the cardiotoxic factors of the veratrum derivatives have been eliminated. The development of tolerance is common, and this limits the usefulness of these compounds.

The hydrogenated ergot derivatives [28, 29] such as dihydroergocornine (DHO) and Hydergine are much more active parenterally than on sublingual or oral administration. Tolerance also develops quickly, and the necessity for parenteral administration limits the usefulness of these preparations. The direct constricting action of these compounds on the smooth muscle of arterioles is light,[30] but if this effect is cumulative it might, theoretically at any rate, contraindicate prolonged therapy.

1-Hydrazino-phthalazine, which is well absorbed on oral administration, has been recently introduced under the trade name of Apresoline.[31, 32] Dosage in milligrams per kilogram is considerably greater than that needed with protoveratrine or Hydergine. Headache, postural hypotension, nausea and vomiting are common transient side actions which do not limit the use of the drug. Drug fever or psychosis precludes its use, although these effects fortunately are uncommon. An interesting effect is transient edema, the mechanism of which is uncertain. Tolerance to this drug is common after three or four weeks of treatment; however, interruption of treatment for one week may restore its effectiveness.

The only drugs known to act at the third motor synapse level in the spinal cord are intraspinal procaine or other intraspinal anesthetics. These have no practical value in the treatment of hypertension but have been used at times for testing purposes to estimate the effect of subsequent sympathectomy.[33]

The fourth motor synapse level, in the autonomic ganglia, however, is amenable to attack with drugs and several have been in use in recent years. If these drugs are used either for testing purposes or in the treatment of hypertension, care must be exercised to exclude pheochromocytoma by pharmacologic tests, since these substances may provoke the secretion of large amounts of epinephrine and nor-epinephrine from such tumors.[34] The first such substances introduced were the tetraethylammonium salts, typified by TEAC.[35, 36, 37] This is an effective parenteral ganglionic blocking drug that has the disadvantage of rapid excretion and hence short duration of effectiveness. Side actions are tingling, postural hypotension, mydriasis,

nausea, vomiting and, occasionally, collapse. The maximal dose that can be given intravenously with safety is 5 mg. per kilogram. Death has been produced by larger doses.[38] The drug may also potentiate the action of insulin and produce insulin shock in diabetics. It is useful for testing but not for the treatment of hypertension, except, perhaps, for hypertensive crisis. Ro 2–2222 is a thiophanium derivative similar in its action and duration of effect to TEAC.[39]

The quaternary amines (SC 1950) [40] and Pendiomide [41] also block autonomic ganglia and are free of the unpleasant tingling seen with TEAC. They are effective parenterally, moreover, in dosage of 0.8 mg. per kilogram, and the duration of their action is less transient than that of TEAC. The only side actions observed on intravenous injection have been dry mouth, occasional nausea and mild postural hypotension. We now prefer these compounds to TEAC for testing, although they are less useful than the methonium compounds for the treatment of hypertension.

Pentamethonium and hexamethonium bromide or chloride [42, 43, 44, 45, 46, 47, 48] are among the most useful drugs for controlling hypertension, largely because of their slow excretion and prolonged effectiveness. They are effective in dosages ranging from 0.1 to 1 mg. per kilogram parenterally. Side actions are rare and consist chiefly of postural hypotension and collapse if too large a dose is given. Hexamethonium bromide may be self-administered by subcutaneous injections if dosage is built up gradually. It is less useful for testing purposes because of the unpredictability of the effect of intravenous injection, and because small doses may produce shock without the collateral signs of shock such as tachycardia and sweating. Norepinephrine and epinephrine are active antidotes, whereas changing position by tilting the body head downward is not always effective. The prolonged action of the drug also makes it less desirable for a testing procedure of one hour's duration.

This drug has also been administered orally,[49, 50] and is effective in dosage of 3 to 9 gm. daily. This implies the absorption of less than 1/100th of the dose given. If an enteritis or acute appendicitis should cause sudden absorption of more than this the effect might be disastrous. Also, the local action of the drug on the ganglia in the intestinal wall is frequently associated with obstipation, which, more rarely, may be followed by intractable paralytic ileus. For these reasons it is felt that oral administration of the drug should be withheld until experience is wider. The chloride has been used orally in preference to the bromide because of the appearance of bromism with large doses. The bromide may, however, be used parenterally because the dosage of the ion is too small to produce undesirable effects as a rule.

There is also a group of drugs which act by blocking discharge at sympathetic nerve endings. Dibenamine [51] and Dibenzyline [52, 53] are in this group, although these drugs are more effective parenterally than on oral

administration. Their side actions consist of nasal congestion, postural hypotension, nausea, vomiting and shock. They are not in general use for the treatment of hypertension largely because of the irregular response to their oral administration, as well as the probable development of tolerance. Also, sympathomimetic drugs are not effective antidotes because their action is blocked by these drugs. Such imidazoline compounds as Regitine [54, 55] and Priscoline [56] also have blocking effects on sympathetic nerve endings. They are rarely used for the treatment of hypertension because Priscoline acts chiefly on capillaries, whereas Regitine has only recently become available for oral administration. The latter drug,[55] and also Piperoxan (Benzodioxane),[57] which is related to Dibenamine, are frequently used as phar-

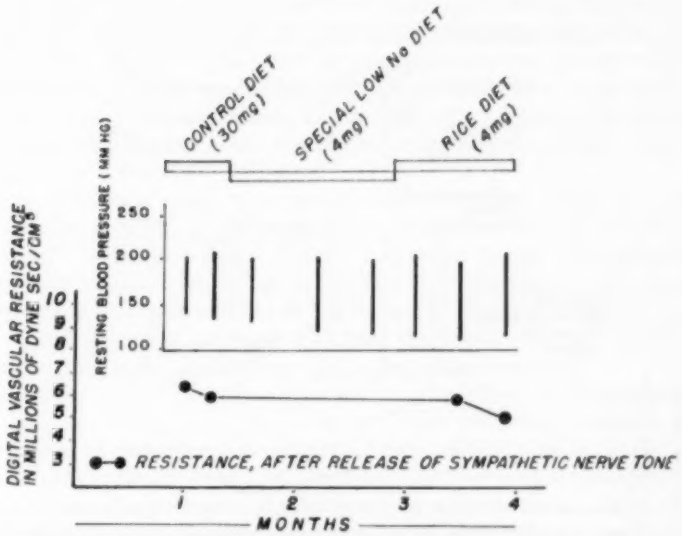

FIG. 2. The effect of dietary salt depletion on the blood pressure and the digital vascular resistance (Eurman and Mendlowitz [59]).

macologic tests for pheochromocytoma because they block the action of circulating epinephrine and nor-epinephrine on the blood vessels.

Direct block of the contraction of smooth muscle of blood vessels is effected by the nitrites and the xanthine group of drugs.[21, 22] Unfortunately, effective oral doses usually produce nausea and vomiting, so that these drugs are relatively ineffective in hypertension.

Drugs which dilate capillaries directly, such as Priscoline and histamine,[21, 22] have little usefulness in hypertension since the vasoconstriction of this disease is chiefly arteriolar. Other drugs act indirectly on the tissues and their blood vessels via salt and water metabolism or oxidative mechan-

isms, and these may produce vasodilatation, presumably because of a decrease in intrinsic or non-neurogenic vascular resistance. The low sodium diet [58] may have such an effect (figure 2),[59] for example, and diuretics, exchange resins and digitalis may all have some effect on vascular resistance in this way.[21, 22] The thiocyanates [60] are also believed to act in this indirect manner, although again side effects of encephalitis, glossitis, stomatitis and agranulocytosis limit the usefulness of these preparations.[21, 22]

From a practical standpoint, it is very helpful to determine the nature of the hypertension in each individual case in order to assess what can be expected with various types of therapy. We have been employing the digital circulation as a test region largely because of the simplicity and convenience of the methods involved.[61] The neurogenic factors are exaggerated in this

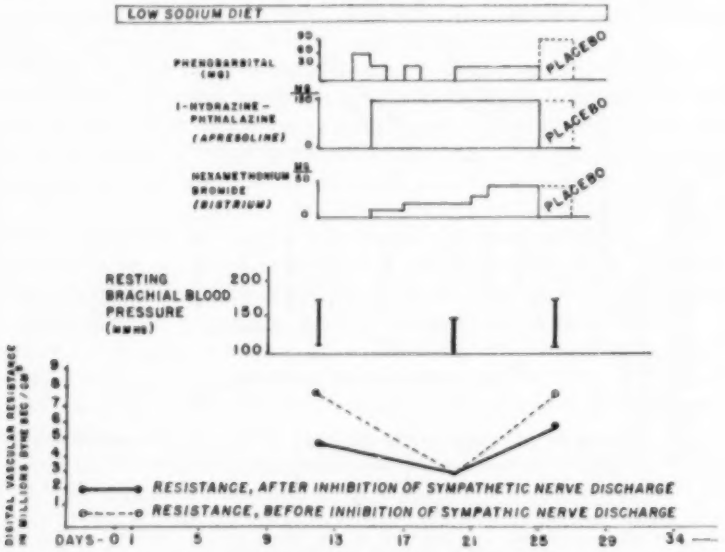

FIG. 3. The effect of drugs on the blood pressure and digital vascular resistance (Eurman and Mendlowitz [59]).

vascular bed, whereas changes in the intrinsic resistance seem to be parallel to similar changes in the systemic circulation as a whole. The flow-pressure ratio is measured before and after inhibition of sympathetic nerve discharge by a standard procedure consisting of the application of heat to the body until sweating or a positive heat balance is achieved, followed by the injection of 0.8 mg. per kilogram of SC 1950 intravenously. It has been shown that this ratio is rectilinear when measured at different pressure levels and hence a good index of vascular caliber, especially after inhibition of sympathetic nerve discharge. Flow is measured calorimetrically.[61]

If the hypertension is largely neurogenic, the drugs of choice at the

present time are 1-hydrazino-phthalazine or protoveratrine orally, combined with hexamethonium bromide by subcutaneous injection two or three times daily (figure 3). Night doses are theoretically undesirable because sleep itself inhibits sympathetic nerve discharge. Phenobarbital may also be used, and antihistaminics may be needed to combat nasal congestion. The possible rôle of Rauwolfia serpentina has not yet been defined. Dosages should be controlled to bring the blood pressure down to but not below the previously determined "floor" for inhibition of neurogenic vasomotor tone. Going below this level usually involves a decrease in cardiac output, with potentially undesirable effects such as azotemia, weakness, etc. For purposes of orientation, testing should be repeated from time to time while the patient is on the drug and also while on placebo therapy.

If the hypertension is largely non-neurogenic, all these preparations have minimal effects and the potential dangers of their administration increase. In such cases, usually in the more severe hypertensives, therapy should be directed toward decreasing the intrinsic resistance, if that is possible. Salt depletion by diet, resins, diuretics, etc., are rational measures despite the knowledge that a residue of structural narrowing of blood vessels will remain even when such therapy is effective.

Very often both factors are present, and salt depletion must be combined with therapy directed at the neurogenic factor for the best results. Salt depletion is ineffective unless rigidly controlled by the determination of sodium and chloride in the urine periodically, combined with occasional determination of serum sodium and potassium. Also, it requires weeks to produce salt depletion adequate to affect the blood pressure significantly, contrary to the prompt effects seen in congestive heart failure.

Tolerance to the effects of Apresoline is common, of hexamethonium less common. Drug tolerance, however, must be distinguished from the development of increased intrinsic resistance, which may occur as a consequence of ganglionic block by drugs as well as after sympathectomy.[17] The operation should be reserved for those patients with a demonstrably large neurogenic element in whom adequate drug and diet therapy has failed.

It cannot be overemphasized, however, that in many cases hypertension requires no treatment. This is especially true of hypertension in the aged,[83] and of the hypertension of advanced renal disease. It is our rule in such cases to treat the complicating effects of hypertension where these exist rather than the high blood pressure itself. Expensive and hazardous treatment with drugs or by operation can be justified in an individual case only if, in the physician's judgment, the pace of the disease represents a threat either to the patient's life or to his continued well-being.

Summary and Conclusions

The treatment of hypertension should be undertaken only when that disease under observation represents a hazard to a patient's life or health.

Drug therapy is usually directed at the neurogenic factor. A variety of drugs is available for blocking the motor synapses and nerve endings concerned in the excessive sympathetic nerve discharge believed to be a factor in hypertension. For the best results this should be defined by testing procedures in advance of and during treatment. The limiting factors are usually tolerance and side actions. At the cortical level, barbiturates are the most useful drugs, although these may be replaced eventually by Rauwolfia serpentina. At the hypothalamic level, 1-hydrazino-phthalazine and protoveratrine are the most effective, whereas at the ganglionic level, hexamethonium bromide or chloride is the drug of choice. Parenteral administration of this drug is preferred to oral administration because of the inherent serious dangers of the latter. Block of sympathetic nerve endings, smooth muscle or of capillaries is at present of minimal practical value in the treatment of hypertension. Salt depletion by diet and dietary adjuvants appears to affect the non-neurogenic or intrinsic factors in hypertension. Sympathectomy should be reserved for patients with a large neurogenic element who fail to respond to adequate medical therapy. In many cases, judiciously combined treatment provides the most satisfactory results.

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MORTALITY RATES IN ACUTE MYOCARDIAL INFARCTION. I. THE "NORMAL" YEARLY VARIATION, AND THE EFFECT OF HOSPITAL ADMISSION POLICY *

By SIDNEY SCHNUR, M.D., F.A.C.P., *Houston, Texas*

THE mortality rate in acute myocardial infarction has been reported as ranging from 8 per cent [1] to 78 per cent.[2] Apparently this wide variation in rates in selected groups is not well appreciated. Several investigators have reached conclusions concerning the value of a particular drug or procedure in this disease solely from finding a low mortality rate in a series of patients,[3, 4] or by noting a decrease in the mortality rate one year as compared with previous years.[5, 6, 7, 8] Because of the increasing number of reports concerned with the effect of specific therapies upon the mortality rate in acute myocardial infarction, a study was undertaken to clarify certain basic facts regarding mortality rate statistics. This report is concerned with one aspect of this study, i.e., the "normal" yearly variation of rates in several hospitals in a single community during a 10 year period, and the effect upon the mortality rate of patient selection resulting from hospital admission policy.

METHODS AND MATERIALS

The mortality rate for acute myocardial infarction for each year from 1941–1950 was determined in four Houston hospitals. The diagnosis was made by the usually accepted criteria. Except for a number of instances in 1948, 1949 and 1950, anticoagulant therapy was not prescribed. During this decade, patients were not actively treated for shock nor were they allowed to sit up in accordance with the suggestion of the "armchair treatment" advocates. The difference in mortality rates, therefore, cannot be attributed to any of these recently recommended therapeutic measures.

RESULTS

The mortality rate for each year for each hospital is noted in table 1. The yearly rates range from 40 per cent to 71 per cent at Jefferson Davis Hospital, 28 per cent to 48 per cent at St. Joseph's Hospital, 24 per cent to 46 per cent at Methodist Hospital, and 0 per cent to 21 per cent at Southern Pacific Hospital. In spite of the wide variation in yearly rates in each hospital, all are within the limits expected from the usual binomial assumption ($2.5 \times$ sigma), and thus may be attributed to sampling. The average

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From the Department of Medicine, Baylor University College of Medicine, and the Jefferson Davis, St. Joseph's, Methodist and Southern Pacific Hospitals, Houston, Texas.

mortality rate for the decade ranged from 52 per cent at Jefferson Davis Hospital to 10 per cent at Southern Pacific Hospital. These mortality rates differ significantly from the average of the entire series (34 per cent). Evidence that unequal selection of patients, i.e., a dissimilarity in the propor-

TABLE I

Yearly Mortality Rates from Acute Myocardial Infarction in Several Hospitals in a Single Community, 1941–1950

Year	Jefferson Davis Hospital	St. Joseph's Hospital	Methodist Hospital	Southern Pacific Hospital
1941	57 (10.8)	39 (7.6)	40 (5.0)	17 (7.7)
1942	50 (11.2)	48 (6.4)	42 (4.8)	8 (4.0)
1943	65 (9.9)	47 (6.3)	41 (4.4)	17 (8.8)
1944	53 (8.5)	32 (5.4)	36 (4.2)	15 (9.9)
1945	71 (8.1)	31 (5.5)	35 (4.8)	0 (2.0)
1946	40 (7.3)	35 (5.7)	46 (6.2)	21 (7.6)
1947	43 (6.8)	28 (5.2)	30 (5.2)	9 (4.8)
1948	45 (9.0)	40 (5.8)	38 (5.1)	4 (2.9)
1949	61 (8.5)	41 (5.2)	24 (4.8)	8 (4.3)
1950	57 (8.0)	43 (4.6)	30 (4.4)	16 (5.8)
Average	52 (2.8)	38 (1.8)	32 (1.5)	10 (1.7)

Figures in brackets denote sigma.

tion of cases seriously ill on admission to the hospital, may be responsible for these interhospital differences in rate and also may influence yearly rates at the same hospital has been presented in other reports [9, 10, 11] in which the severity of illness on admission to the hospital was measured quantitatively

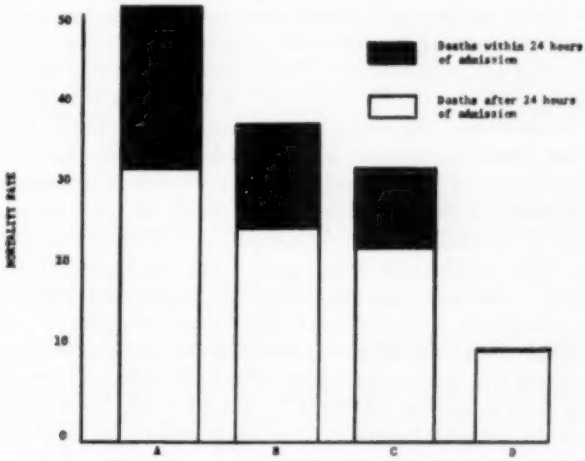

FIG. 1. The average mortality rate in Jefferson Davis (A), St. Joseph's (B), Methodist (C), and Southern Pacific (D) Hospitals with the portion due to deaths occurring within the first 24 hours following admission to the hospital.

by a method of scoring termed the Pathological Index Rating.* Figure 1 graphically depicts the portion of the total mortality rate due to deaths within 24 hours of admission in each hospital.

Discussion and Conclusions

Jefferson Davis Hospital is a City-County charity hospital with an active emergency service which, b cause of a shortage of beds, admits only seriously ill patients, and where predominantly seriously ill patients seek admission. This hospital had the highest mortality rate (52 per cent) and the highest proportion of deaths (30 per cent) within 24 hours. St. Joseph's Hospital is a private hospital with a large emergency service, and the mortality rate averaged 38 per cent. Methodist Hospital is a private hospital with no emergency service, and its rate was found to be 32 per cent. Southern Pacific Hospital is a private hospital for railroad employees. Preventive medicine is practiced extensively, and generally these employees are in the prime of life. Many patients are admitted for convalescence after having been treated elsewhere for the acute phase of their infarction. This eliminated the critically ill, the majority having died prior to transfer. In addition, patients are admitted for evaluation of their physical condition prior to return to work following recovery. This hospital had an average mortality rate of 10 per cent, and in one year (1945) there were no deaths from this disease.

Each hospital apparently has an average mortality rate from acute myocardial infarction which is determined by its selection of patients, and is a reflection of its admission policy and the type of patients treated. The yearly rate varies widely, and depends primarily upon the chance variation of small samples, and partly upon the proportion of seriously ill patients admitted for that particular year. This would indicate that any study which attributes a decreased mortality rate to a new therapy solely on the basis of a difference in mortality rate from a preceding year is likely to be in error because of the extreme "normal" variation of rates from year to year due to these factors. Even a "statistically significant" difference may be due to a primary inequality of the groups being compared, rather than to the experimental drug or procedure under investigation. Unless this fact is clearly recognized, false conclusions may result from an apparently "statistically proved" study. For example, the "decrease" in the mortality rate reported by various hospitals following the institution of routine anticoagulant therapy may have been caused partly by a shift in the hospital population due to the admission for specific treatment of mildly ill patients who previously would have been cared for at home.[11] In addition, these findings would suggest that the hospital mortality rate alone cannot be used as a gauge of

*This does not imply that an individual patient's prognosis is not affected within certain limits by the quality of medical and nursing care and the proper use of various therapeutic measures. Actually, in most discussions of the mortality rate in this disease, especially following the new drugs or procedures, these factors are apt to be emphasized, whereas the equally important "patient factor" is often disregarded or minimized.

the professional competence of the attending staffs because of the vast differences in the seriousness of the patient's illness on entrance into various hospitals, determined in large measure by admission policy.

Summary

1. The yearly mortality rate from acute myocardial infarction in four hospitals in a single community during the decade 1941–1950 was determined.

2. A wide variation of rates from year to year in each hospital was noted, but the average rate for the decade appeared to be determined in large measure by the hospital's criteria and policy for admission and the type of patients treated.

3. Conclusions concerning the effectiveness of a new drug or procedure drawn solely from finding a decreased mortality rate one year as compared with previous years must be viewed with suspicion because of the wide "normal" fluctuation of rates from year to year due to the chance variation of small samples and the constantly changing proportion of seriously ill patients admitted.

4. The hospital mortality rate cannot be used as a gauge of the professional abilities of the attending staff, nor can the rates of different hospitals be used to compare competence in the treatment of this disease because of the difference in severity of illness of patients admitted to various hospitals.

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MORTALITY RATES IN ACUTE MYOCARDIAL INFARCTION. II. A PROPOSED METHOD FOR MEASURING QUANTITATIVELY SEVERITY OF ILLNESS ON ADMISSION TO THE HOSPITAL *

By SIDNEY SCHNUR, M.D., F.A.C.P., *Houston, Texas*

IN any clinical investigation whose purpose is to gauge the effect of therapy upon the mortality rate, it is axiomatic that treated and control groups must first be equivalent in all factors affecting prognosis if the study is to yield sound and valid conclusions. This would be especially true in a disease such as acute myocardial infarction, in which the mortality rate has been reported to range from 8 per cent [1] to 78 per cent.[2] Unfortunately, the large number of prognostic factors in this disease has made it difficult to determine whether two groups are in fact equal. The solution of this problem would be of inestimable value to investigators in the field of therapeutics, and probably would result in publication of a higher proportion of papers in which the validity of the conclusions would not be open to debate.

The recent literature on the effect of routine anticoagulant therapy upon the mortality rate in acute myocardial infarction reveals the difficulties inherent in this type of investigation and illustrates studies leading to questionable conclusions. Thus, some workers reach definite conclusions concerning the efficacy of anticoagulants without using controls.[3, 4] Others discuss factors in the treated and control groups not closely enough related to prognosis to be considered valid,[5] or describe the composition of their groups in qualitative terms, i.e., mild, moderate, severe.[6] Such qualitative descriptions without definite measurable criteria, especially when made by many different clinicians, are likely to be inaccurate and therefore unsatisfactory.[7] A common practice is to compare the mortality rate of treated cases one year with untreated cases of a preceding year or years, under the mistaken assumption that this provides "adequate controls." [5, 8] Because of the wide "normal" variation of rates from year to year, conclusions derived from such studies must be carefully evaluated.[9] A useful statistical method, especially applicable when many factors are involved and large numbers of patients are available, is to place alternate cases or those admitted on odd and even days into control and treated groups. Such procedure may produce equivalent groups if the number of subjects is large, and, most important, if patients are placed in the designated groups absolutely according to rule, without

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From the Department of Medicine, Baylor University College of Medicine, and the Jefferson Davis Hospital, Houston, Texas.

allowing personal or other preferences to influence the selection.[9] Wright's [6] series was adequate in size but apparently was not selected completely at random, and thus his conclusions are questionable.[10] * Tulloch and Gilchrist's [11] excellent study using the same technic unfortunately consisted of too few cases (84 cases in control series and 74 cases in the treated). These investigators determined the number of patients in each group with a history of angina, hypertension, previous myocardial infarction, obesity, degree of functional capacity, and those who presented clinical evidence of shock, heart failure, arrhythmias and thromboembolic phenomena. By their emphasis on the "patient component," the authors have reaffirmed the obligation of all investigators to compare treated and control groups for all factors intimately related to prognosis prior to starting therapy. It is only when these groups are initially equivalent from the prognostic standpoint that consideration can be given to the statistical significance of a difference in mortality rate resulting from the use of an experimental procedure or medication. If the groups are prognostically unequal, sound conclusions can not be obtained, because a "statistically significant difference" may be attributed to the original disparity between the groups rather than to the therapy employed.

It would appear that a preferred method of determining prognosis would be one which could quantitatively grade the severity of illness of each patient on admission to the hospital, the rating or score to be the sum of all findings known to influence prognosis and each to be correctly weighted for its relative importance in causing death. Such a laudable aim is unattainable at present because of disagreement concerning the significance of certain factors,[12, 13] and, most important, because the relative weight of each factor cannot be accurately gauged due to the large numbers present in each case making it difficult to isolate the effect of each.[14] However, in spite of the obvious difficulties, it was thought advisable to initiate such a project primarily to determine its feasibility. A study was therefore undertaken to grade numerically the severity of illness of patients entering the hospital with acute myocardial infarction and to investigate several problems by this approach. This report on the correlation of the patient's condition on admission with the mortality rate is presented for the purpose of indicating the actual and potential value of this method of study. Detailed reports of other investigations utilizing this technic have been published elsewhere.[9, 20]

Methods and Materials

The clinical records of patients admitted to Jefferson Davis Hospital for acute myocardial infarction between 1941–1950 were reviewed. The records in which the diagnosis could be reasonably substantiated from the

* Additional clinical and statistical objections to this study are presented in other reports.[9, 20]

electrocardiogram, clinical examination, history, clinical course or postmortem examination were analyzed; for the purpose of this report, patients dying within 24 hours of admission were not included. This study is concerned with 230 admissions.

By a predetermined formula, certain specific admission findings and historical data were assigned a numerical value (table 1). The factors con-

TABLE I

Information Obtained from Clinical Records, Ratings for Various Clinical Findings, and Method of Determining Pathologic Index Rating

Information Obtained from Clinical Records

Date of Admission	Congestive Heart Failure
Age	Serious Arrhythmia
Sex	Associated Serious Diseases
Results (Lived or Died)	Pulmonary
Died (Within 24 Hours or Later)	Renal
Shock	Other
	History of Serious Vascular or Other Disease

Pathologic Index Ratings

Shock		40	Associated Serious Diseases		10–25
			Diabetes	10–25	
Congestive Failure		20–25	Uremia	10–25	
			Urinary Tract Infections	10	
Serious Arrhythmias		10–40	Emphysema	10	
Occasional Ventricular Contraction	10		Cerebral Thrombosis	10–25	
Frequent Ventricular Contraction	15		History of Heart or Vascular Disease		10–30
Auricular Tachycardia	15		Hypertension	10	
Auricular Fibrillation	25		Cardiac Enlargement	15	
Auricular Flutter	30		Angina	10–30	
Ventricular Tachycardia	40		Congestive Failure	20–30	
Gallop Rhythm		15	Previous Coronary Occlusion	20–30	

EXAMPLES:

Patient entered in shock (40) with history of previous hypertension (10) and mild diabetes (10): Pathologic Index Rating = 60.

Patient entered in shock (40), congestive failure (20) and ventricular tachycardia (40) with history of hypertension (10) and previous severe coronary occlusion (30): Pathologic Index Rating = 140.

Patient entered with negative findings (no shock, congestive failure, arrhythmia or associated serious disease) with history of hypertension (10): Pathologic Index Rating = 10.

sidered significant were based upon previous studies of factors known to influence the mortality rate, and the actual number assigned to each factor was determined by the author's clinical estimate of the relative importance of each in the prognosis, using former studies [1, 15, 16, 17, 18] as a guide.* Al-

* Only those factors were considered which could be immediately determined at bedside examination. Laboratory and ancillary aids, some of which are of prognostic value, were not included. The addition of these in future studies would probably increase the accuracy of the ratings. Another important factor is the completeness of the clinical records from which the data are collected, especially when the information is obtained in retrospect.

though this is admittedly somewhat inexact (and others may wish to add other factors or weight them somewhat differently), the advantage of this quantitative determination is that all patients evidencing the same clinical findings receive the same rating, no matter whether they are in another group, another hospital or another city, and those findings which are of greater prognostic significance are given greater weight in the final summation. Shock was considered to be the most serious state and was given a maximal value of 40. This number had no special significance—any num-

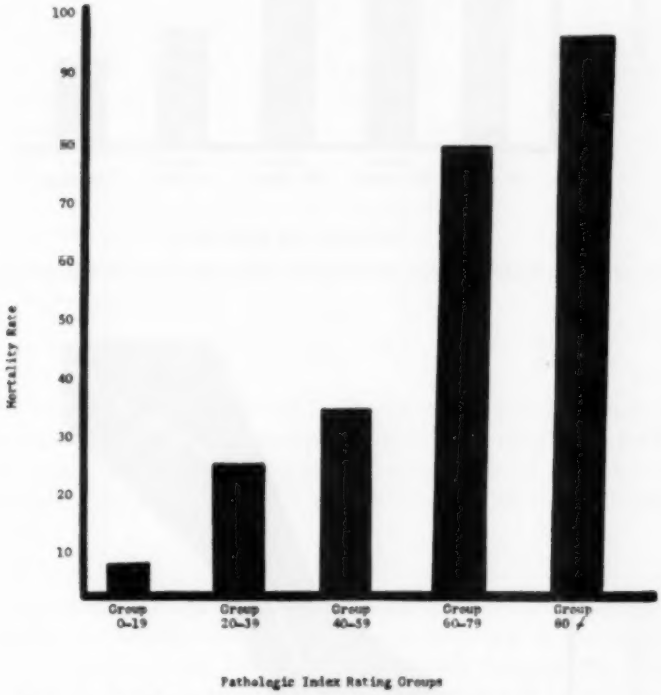

FIG. 1. Mortality rate in different pathologic index rating groups.

ber could have been chosen. With this as a basis, the clinical findings and historical data listed in table 1 were given values according to what was considered their relative importance in causing death. The sum of these in each patient was designated the pathologic index rating. This rating was a quasi-quantitative measure of the severity of the disease and the clinical status on admission, prior to institution of therapy. In this study the pathologic index rating ranged from 0 to 140. For ease of statistical analysis, patients were placed in one of five pathologic index rating groups;

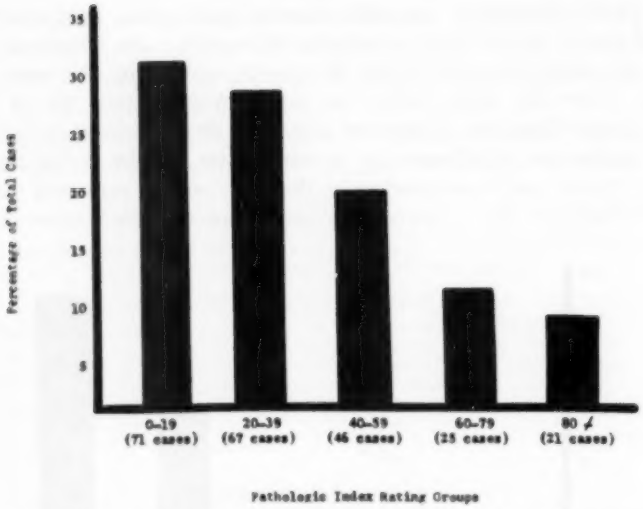

FIG. 2. Distribution of cases according to pathologic index rating groups.

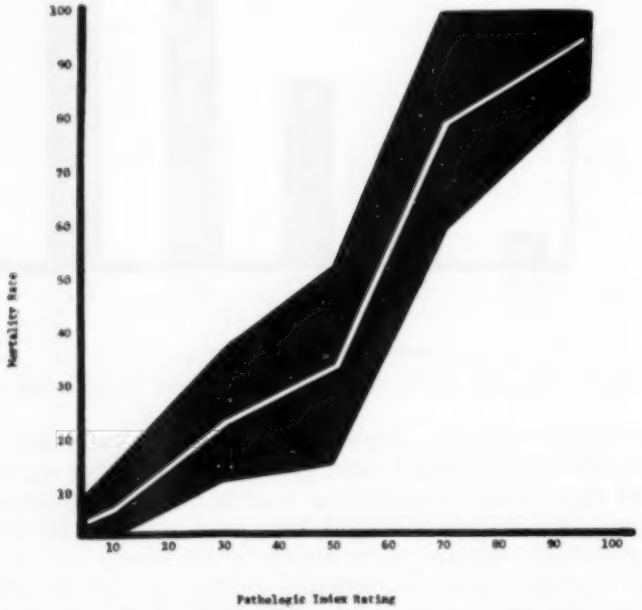

FIG. 3. Correlation of mortality rate with pathologic index rating. Shaded area includes $\pm 2.5 \times$ sigma ($P < .01$).

TABLE II

Comparison of Pathologic Index Rating, Average Age and Sex Ratio in Years of Highest (1945) and Lowest (1946) Mortality Rates

Pathologic Index Rating Groups	1945			1946		
	Cases	Deaths	Mortal. Rate	Cases	Deaths	Mortal. Rate
0–19	6	1	17%	11	1	9%
20–39	4	1	25%	16	3	19%
40–59	3	2	66%	5	2	40%
60–79	12	12	100%	8	8	100%
80+	6	6	100%	3	3	100%
Total	31	22	71%	43	17	40%
Mortality Rate*		71%			40%	
Per Cent of Total Deaths Within 24 Hrs.		45			23	
Average Age		56			58	
Per Cent Males		80			76	

* Standard error of the difference is 11 $P < .01$

Distribution of Patients According to Pathologic Index Rating Groups

Pathologic Index Rating Groups	1945	1946
0–39	33%	63%
60+	58%	26%

viz., 0 to 19; 20 to 39; 40 to 59; 60 to 79, and 80 and above. These groups reflected gradations in severity and would correspond roughly to the clinical classifications mild, moderate, moderately severe, severe, and critically ill. The mortality rate and number of patients in each of these groups were determined.

RESULTS

The mortality rate and number of cases in each of the pathologic index rating groups in Jefferson Davis Hospital for the entire 10 year period are presented in figures 1 and 2. Excluding patients dying within 24 hours of admission to the hospital, the rate ranged from 8 per cent in the 0–19 (mild) group, to 95 per cent in the 80-plus (critically ill) group. These findings are shown graphically in figure 3. The distribution of cases according to pathologic index rating groups for the years 1945 and 1946 (table 2) indicates the variability in the severity of illness of patients admitted from year to year and its effect upon the mortality rate.

CONCLUSIONS

The prognosis of the patient with acute myocardial infarction is determined to a large extent by the severity of illness upon admission to the

hospital.* In the mildest group the mortality rate was 8 per cent, whereas the most severely ill had a 95 per cent mortality rate. If the pathologic index rating included all the factors affecting mortality, and each was accurately weighted, it is probable that a mathematically precise straight line relationship or parabolic curve might be found to exist between the seriousness of illness on admission and the mortality rate. In the study of a group which would correspond to a pathologic index rating of 0, Russek [19] found the mortality rate to be 3.1 per cent. The theoretic curve might therefore be a straight line or quadratic parabola between 3 per cent mortality for a pathologic index rating of 0, to 95 per cent mortality for a pathologic index rating of 95. The shaded area (figure 3) indicates the chance scattering of mortality rates due to sampling.

Thus, all other things being equal, a decrease in the mortality rate following the use of any new therapeutic measure in this hospital could not be considered statistically significant unless the mortality rates of sizable groups of patients fell fairly consistently below the shaded area.† This type of study would also determine whether the therapy was effective in patients with all degrees of illness, or was limited to a specific group such as the seriously ill. It may also be predicted that each hospital will have its own basal curve somewhat similar to that depicted for Jefferson Davis Hospital. Any significant divergence from the "normal" universal graph might indicate the hospital staff's relative success in the treatment of this disease, or other presently undisclosed general patient factors.[20]

Summary

1. The importance of developing a method for estimating quantitatively the severity of illness of patients with acute myocardial infarction on admission to the hospital was discussed.

2. An attempt was made to accomplish this aim by devising a scoring system termed "Pathologic Index Rating."

3. The Pathologic Index Rating was found to be closely related to the mortality rate, ranging from 8 per cent in the group with the lowest rating to 95 per cent in the group with the highest rating.

4. The correlation between these factors was represented by a graph, and a somewhat similar "normal" curve for each hospital was predicted.

* This does not imply that an individual patient's prognosis is not affected within certain limits by the quality of medical and nursing care and the proper use of various therapeutic measures, matters which require no discussion. This study is concerned with the "patient factor," one which is often disregarded or minimized. The rating is also not to be interpreted as indicating whether a specific patient will live or die, but rather as a more objective means of determining the mathematical probability of such event's occurring.

† The standard error of the difference would have to be computed, but for the purpose of this discussion this statement is acceptable. Statisticians have other and better methods to determine significance accurately. This method is presented primarily to visualize for those not interested in the details of statistical analysis the concept of "normal" variation from the mean as it may be applied to mortality rates in specific Pathologic Index Rating groups.

5. This method might be useful in the design of a controlled experiment in which patients could be paired on the basis of their index, and then assigned at random to treated and control groups, rather than the usual method of simple alternation of pairs without regard to severity of illness.

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FURTHER OBSERVATIONS ON SMOKER'S RESPIRATORY SYNDROME *

By GEORGE L. WALDBOTT, M.D., F.A.C.P., *Detroit, Michigan*

THE literature concerning the effect of tobacco on the human organism is mainly concerned with the cardiovascular system. In a review on the subject, Scott [1] notes that during smoking the blood pressure shows a transient rise, averaging 15 mm., the pulse rate increases about eight beats a minute, and skin temperature falls due to capillary constriction. Bryant and Wood [2] observed the occurrence of anginal pains from smoking. Smoking is believed by some to be responsible for the occurrence of thromboangiitis obliterans.

Relative to the respiratory tract, there is some evidence—and much speculation—that smoking contributes to the development of lung cancer. In Wynder's [3] series of 684 patients with bronchial carcinoma, only 1.3 per cent were nonsmokers, in contrast with 14.6 per cent in the general hospital population. A reduction in vital capacity during smoking was observed by Whitfield et al.[4] An inflammatory lesion in the larynx was described by Myerson [5] in 143 smokers who complained of hoarseness and vocal fatigue. Literature on respiratory symptoms due to smoking is sparse, yet there is hardly a physician who does not daily see cases with "smoker's throat," "smoker's larynx" and "smoker's lungs," as well as "smoker's cough."

Recently I [6] described a clinically well defined syndrome of respiratory symptoms due to smoking. I have accumulated additional data concerning this syndrome which I wish to present here.

Of 821 patients who consulted me because of suspected allergic nasal and bronchial symptoms, 715 were smokers. Fifty-eight cases (or 7.1 per cent) were observed with manifestations characteristic of smoker's respiratory syndrome. There were 37 men and 21 women, aged 28 to 75. In eight additional cases with advanced pulmonary emphysema, there was presumptive evidence that their condition was due to smoking.

DIAGNOSIS

Smoker's "asthma" is characterized by a clear-cut triad of symptoms, namely, (1) chronic pharyngitis, (2) wheezing and dyspnea, and (3) a tendency to respiratory infections, with and without fever. Table 1 shows that this triad of symptoms was noted in all 58 cases. The most characteristic and constant feature which may lead to a spot diagnosis of the syndrome is the chronic inflammation of the pharyngeal mucosa and of the

* Presented at the Thirty-Fourth Annual Session of the American College of Physicians, Atlantic City, New Jersey, April 17, 1953.

TABLE I

Symptoms in 58 Cases of Smoker's "Asthma"

	Extensive	Slight	Total
Wheezing	11	47	58
Chronic pharyngitis	39	19	58
Cough and expectoration	27	31	58
Dyspnea on exertion	12	20	32
Chest pains	7	25	32
Constriction in chest	5	26	31
Frequent, acute sore throats	20	38	58
Bronchial and pulmonary infections		febrile	31
Bronchial and pulmonary infections		afebrile	19
Hoarseness	5	12	17

tonsillar area. The pharyngeal mucosa shows a persistent hyperemia. It is usually fiery red and occasionally covered with mucopurulent material. Small lymphoid nodules appear on the pharyngeal wall; perhaps they are the equivalent of the lesions described by Myerson in the larynx. Asthma-like wheezing, cough and expectoration are most pronounced in the morning, not, as might be expected, at the time when the patient does most of his smoking. Dyspnea on exertion occurs in about one-half of the cases. It is usually not very intense, but may in some cases dominate the clinical picture. Chest pains are rhythmic, darting and angina-like in character; they occur in practically any part of the lungs, and around the heart and hypogastrium, radiating into the neck and arms. They are associated with a sensation of precordial constriction. Laryngoscopic examinations on seven cases revealed Myerson's lesions in the larynx in three. The history of frequent respiratory infections is borne out by x-ray findings. They

TABLE II

Differentiation of Smoker's "Asthma" from Bronchial Asthma

	Smoker's "Asthma"	Bronchial Asthma
Wheezing, Localized	In Upper Parts of Lungs and Trachea	Anywhere in Lungs
Respiratory distress	Slight	Marked
Upper respiratory infections start:	In throat and pharynx	In nose and sinuses
Pharynx	Chronic infection	Postnasal drip
Emphysema	Slight in our cases	Extensive
Hoarseness	Common	Not so frequent
Eosinophilia in sputum and blood	Persistently absent	Present
Intradermal skin reactions	Negative	Usually positive
Allergic family and personal background	Negative	Usually positive
Vital capacity	Slightly decreased in our cases	Usually greatly decreased
Bronchoscopic findings	Inflammation in large bronchi; little spasm	Bronchospasm; inflammation through bronchial tree; mucous plugs

reveal an accentuation of the hilar markings, scar formation and pleural adhesions. In some instances areas of infiltration are noted which are somewhat suggestive of cancer; they may disappear upon treatment.

Differentiation from Bronchial Asthma

Smoker's "asthma" can easily be distinguished from allergic asthma (table 2): the paroxysms of wheezing are not nearly so distressing as those of allergic asthma. The patient can sleep lying down, in contrast to the asthmatic patient, who tends to remain in an upright position. The wheezing is localized principally in the tracheobronchial area; in allergic asthma it can appear anywhere in the lungs. The respiratory infections originate in the pharynx or tonsils; in bronchial asthma, they start in the nasal mucous

Table III

Grouping of Cases According to Severity of Symptoms

Group	Number of Cases	Estimated Average Duration of		Estimated Daily Number of Cigarettes*	Relief			Unable to Follow Up
		Illness (years)	Smoking (years)		Complete	Partial	None	
1. Prompt improvement on elimination of smoking	34	3.2	10.1	10 to 15	28			6
2. Additional therapy required	24	7.2	18.7	20 to 30	18	4		2
3. Intractable cases (Presumptive evidence!)	8	18	30.5	20 to 30		3	3	
4. Bronchial asthma combined with smoker's syndrome	18	28†	16	10 to 15	‡			

* All but four patients were cigarette smokers.
† Duration of asthma.
‡ Impossible to determine definitely, since treatment for allergy was given simultaneously.

membranes and sinuses, where we find typical allergic edema and, frequently, polyp formation. These structures as a rule are not involved in our syndrome. Vital capacity reading in 17 of our cases showed an average decrease of only 85 per cent of normal, which is much less than in bronchial asthma. In our syndrome there is no allergic background, no eosinophilia in the blood and in nasal and bronchial secretions; skin reactions for tobacco smoke or tobacco extract are negative; there is no evidence of other sensitizations. However, exposure to such irritants as odors of paint, burning wood, frying fat or grain dust may bring about asthma-like wheezing.

The bronchoscopic examination reveals the same fiery red inflammation in the upper bronchi as noted in the pharynx. The process of inflammation,

however, does not extend far into the ramification of the bronchial tree. There is little or no spasm of the bronchi. The mucus is not so tenacious and thick as in bronchial asthma. In contrast with this, in allergic asthma the bronchial mucosa is less hyperemic and is occasionally pale; there is extensive bronchospasm; the inflammatory process extends down into the lowest ramifications of the bronchi.

Smoker's syndrome is very persistent and remissions occur rarely. This is in contrast with perennial allergic asthma, in which there is usually a tendency to temporary aggravation and temporary amelioration.

Classification of Cases

Our 58 cases could be clearly separated into two distinct groups (table 3) according to their severity:

1. Thirty-four patients manifested symptoms which were promptly reversible upon elimination of smoking. Their condition was not incapacitating. They complained of wheezing in dusty surroundings and upon exertion. In the morning it took them several hours to clear their throats of mucus.

2. The 24 cases of the second group manifested extensive emphysema and wheezing. The sputum was copious and purulent; leukocytosis and an increased sedimentation rate were noted. They suffered marked dyspnea on exertion. Elimination of smoking did not bring relief, and more or less extensive antibiotic treatment had to be resorted to.

The eight patients of a third group manifested irreversible changes. They had been previously diagnosed as cases of "intrinsic" asthma or chronic emphysema of unknown origin. Marked wheezing, dyspnea and cyanosis characterized this condition. It appeared to be the end result of our syndrome. These patients obtained temporary benefit by elimination of smoking, combined with antibiotic treatment, cortisone and bronchoscopic lavages, but in general there was no material change with any form of therapy. Since these patients did not recover with elimination of smoking, no final proof can be offered that smoking was responsible. The following is presumptive evidence for this theory: They gave a history of intensive, chronic smoking habits. All the above described manifestations, especially chronic pharyngitis with chest pains, preceded the present state. Allergic features were absent.

Coincidence with Bronchial Asthma

In patients with allergic asthma who are habitual smokers the clinical characteristics of both conditions, namely, our syndrome and allergic asthma, can be clearly discerned. I observed 18 patients whose allergic asthma could not be controlled until smoking was completely eliminated. Further details on this point will be presented elsewhere.

Mechanism

Positive intradermal reactions to tobacco and tobacco smoke can be obtained frequently among allergic patients. However, a clear correlation of positive skin tests with asthmatic symptoms is difficult to establish. The fact that the 58 cases presented no evidence of allergy and that skin reactions to tobacco were negative indicates that allergy to tobacco played no part in smoker's respiratory syndrome. Instead, it is likely that the symptoms were due to chemical irritation and subsequent inflammation from such irritants as nicotine, pyridine, collidine, ammonia, hydrocyanic acid and carbon monoxide, present in tobacco smoke.

The mucus formed during the course of the chronic inflammation of the mucous membranes leads to partial obstruction of air passages and to asthma-like wheezing. Presence of mucus and perhaps the bronchoconstrictor action of nicotine account for the feeling of constriction, bronchospasm and dyspnea. The obstructing mucus was actually observed at bronchoscopies.

Conclusions

Several conclusions can be drawn from these observations:

1. The condition described here is common. The incidence is much higher than our percentage of 7.1 indicates. This figure did not include all cases with associated allergic symptoms or those with a condition too far advanced to be correlated with smoking.

2. The recognition of this syndrome will prevent patients from undergoing unnecessary allergic studies and therapy. Several cases had been diagnosed on clinical grounds as cases of bronchiectasis. They proved to be smoker's respiratory syndrome and cleared up completely with elimination of smoking. Furthermore, the recognition of this syndrome will aid in clarifying our concept of vague diagnoses such as chronic emphysema and so-called "intrinsic asthma" which so often lead to confusion in our clinical evaluation and to mismanagement of our patients.

As to the treatment of our syndrome, in uncomplicated cases of the first group (table 3) complete and prompt elimination of smoking led, within about seven days, to complete subsidence of symptoms. In the more advanced cases of the second group, cessation of smoking had to be combined with antibiotic treatment. For the patients with irreversible lesions, only supportive treatment can be offered. Since in allergic asthma chronic infection plays a major part, and since in the allergic the bronchial mucosa is very sensitive to irritating gases, complete elimination of smoking is an absolute necessity in asthmatic individuals.

Summary

1. A clinical syndrome is described consisting of chronic pharyngitis, wheezing, dyspnea, chest pains, precordial constriction, and a tendency to

frequent respiratory infections. This was observed in 58 cases, of which 28 recovered completely upon cessation of smoking, 24 upon elimination of smoking combined with antibiotic treatment.

2. Presumptive evidence is offered that this condition leads to chronic emphysema and to so-called "intrinsic asthma." It is held that these secondary changes follow the persistent infections of the upper respiratory tract.

3. When allergic asthma is complicated by our syndrome the asthma does not yield to allergic management unless the patient abstains from smoking.

4. The recognition of this syndrome will eliminate unnecessary diagnostic and therapeutic procedures. It will assist in clarifying our conception of such vague clinical entities as chronic emphysema or "intrinsic" asthma.

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ACUTE IDIOPATHIC PERICARDITIS*

By Edwin M. Goyette, Colonel, M.C., U. S. Army, *Denver, Colorado*

Introduction

Acute idiopathic pericarditis has been recognized with increasing frequency during recent years.[1-4] Because this benign disorder is so frequently confused with acute myocardial infarction, we have been prompted to review our experience with this form of pericarditis at Fitzsimons Army Hospital. During the past three and one-half years we have seen 28 cases that we considered to be of the idiopathic or benign variety. A case was considered of idiopathic etiology only if all known causes, such as rheumatic fever, tuberculosis, myocardial infarction, uremia, tumor, trauma, specific infections, etc., could be eliminated. All but six of these cases were initially diagnosed as myocardial infarctions. The differential diagnosis can be made with reasonable accuracy if the main clinical features are appreciated and kept in mind.

Clinical Features

Acute idiopathic pericarditis is a disease which occurs predominantly in males in a ratio of 2 or 3 to 1. The most usual age period is in the third and fourth decades, but cases in the so-called coronary age period are not infrequent.[4] The age distribution of our cases varied from 18 to 63, with all but four cases being less than 50, and with most of the cases occurring in the third and fourth decades. The age incidence reflects the age distribution of our patient population.

A history of a preceding respiratory infection is common,[1, 3] and was elicited in 17 of our cases; no pertinent information was obtained in six. A history of unusual physical or emotional exertion or exposure to cold is not unusual and occurred in six cases. Some cases follow surgical procedures.[2]

The onset was abrupt in 19, less acute in eight, and insidious in one. The presenting complaint was pain in all patients. The pain was localized in the midchest and substernal region in 17 patients at the onset, in the left anterior chest or precordial region in six, in the chest and back in two, in the left shoulder in two, and in the left arm in one. The pain is usually severe, and closely mimics that of myocardial infarction in character and location. It is usually intermittent but may be persistent, and may be described as sharp or dull, stabbing or aching, pressing, gripping, constricting or oppressive. The pain is usually intensified by respiration, and this feature occurred in

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From the Medical Services, Fitzsimons Army Hospital, Denver, U. S. Army Hospital, Camp Carson, and the Department of Medicine, University of Colorado School of Medicine, Denver, Colorado.

all but three cases. It is commonly aggravated by the prone position or torsion of the body, as was seen in 11, and may be increased by swallowing and coughing. One patient complained of sharp exacerbation of his pain every time his heart beat. Exercise is usually without effect. Radiation of the pain is common, and the sites most frequently involved, in order of decreasing frequency, were the left shoulder, right shoulder, precordium, neck and back. Radiation down the left arm may be noted, but is not usual. The three patients whose pain began in the left shoulder and arm all subsequently had localization in the substernal region. The associated symp-

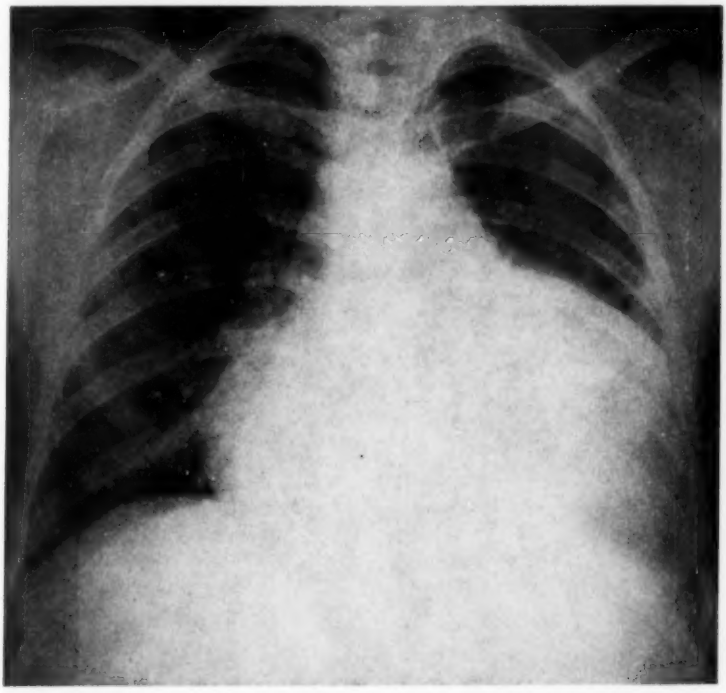

FIG. 1. Chest x-ray showing a massive pericardial effusion.

toms most commonly encountered were malaise, fever, cough, dyspnea and nausea.

It has been emphasized that the physical finding of greatest importance in the diagnosis of this disease is a pericardial friction rub. Its presence within a few hours of the onset of chest pain is a valuable aid in the differentiation of this syndrome from acute myocardial infarction, where such a sign seldom appears within the first 36 hours. A rub was heard in 23 of our cases; the remaining five patients were not seen early in their illness.

In 13 patients the rub was heard at the initial examination, which was performed within 24 hours of the onset of chest pain in 12 patients. The rub is usually audible for several days but may persist for two months, as it did in one of our cases. It may disappear only to reappear a few days later. A loud to-and-fro rub is usually associated with a more prolonged

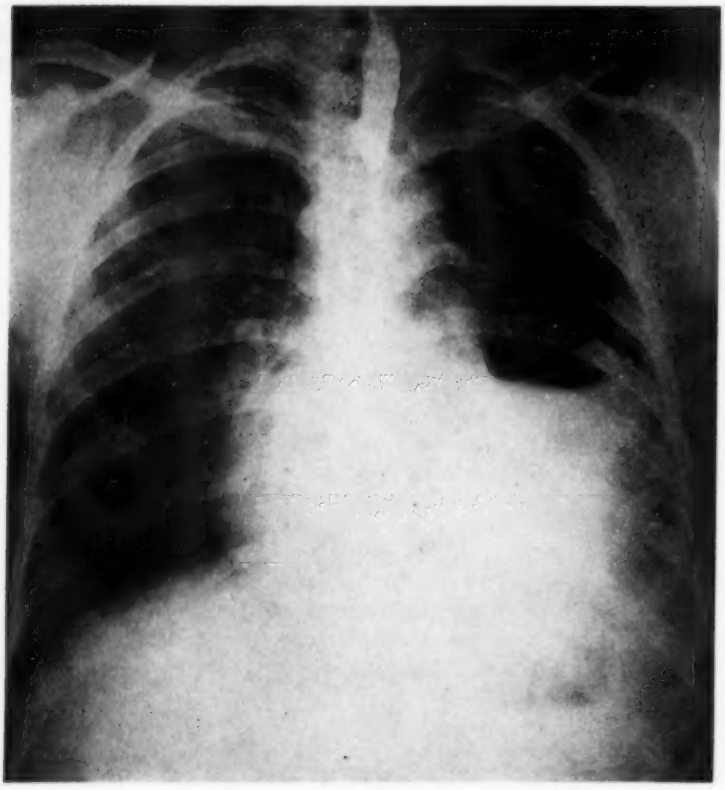

FIG. 2. Same patient after injection of air into pericardium. Note thin, delicate parietal layer.

course.[4] A pleural rub may also be heard. Profuse sweating commonly occurs, but circulatory collapse is unusual and was not seen in any case.

The temperature is almost always elevated at the onset of the illness, as it was in all of our cases but one. The rise varied from 99.6 to 104.6° F. The usual duration of the fever is a few days to a few weeks, but it may persist for two months.

Enlargement of the cardiac shadow occurs frequently.[5] This was due

to a large effusion in two cases, and a small but proved effusion in two others. The other cases of cardiac enlargement are probably due to dilatation, but may be due to the presence of a small effusion. Pleural effusion, more commonly left sided but often bilateral, occurs frequently.[6, 7] Two of our cases had a unilateral, right sided effusion. Figures 1 and 2 show a massive pericardial effusion seen in one patient and figure 3 is the appearance of the chest x-ray after recovery.

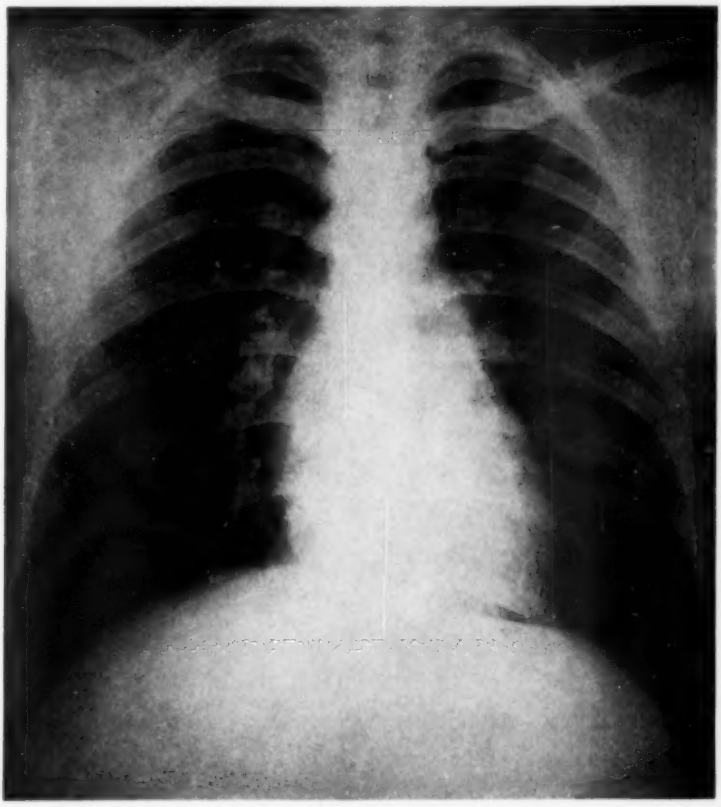

FIG. 3. Same patient after recovery.

Tuberculin skin tests were done on nearly all patients, and the results paralleled the usual incidence in our patient population. Two cases with large effusions had a negative Mantoux test using second strength purified protein derivative. Figure 4 is the chest film of another patient taken before the onset of pericarditis. Figure 5 shows a definite increase in heart size and a bilateral pleural effusion. Three days later (figure 6) the heart size

has returned to the previous width and the pleural effusions have been absorbed.

Laboratory studies are a distinct aid. The erythrocyte sedimentation rate and total leukocyte count are almost always elevated at the onset of the illness. All but one of our cases showed an elevated sedimentation rate,

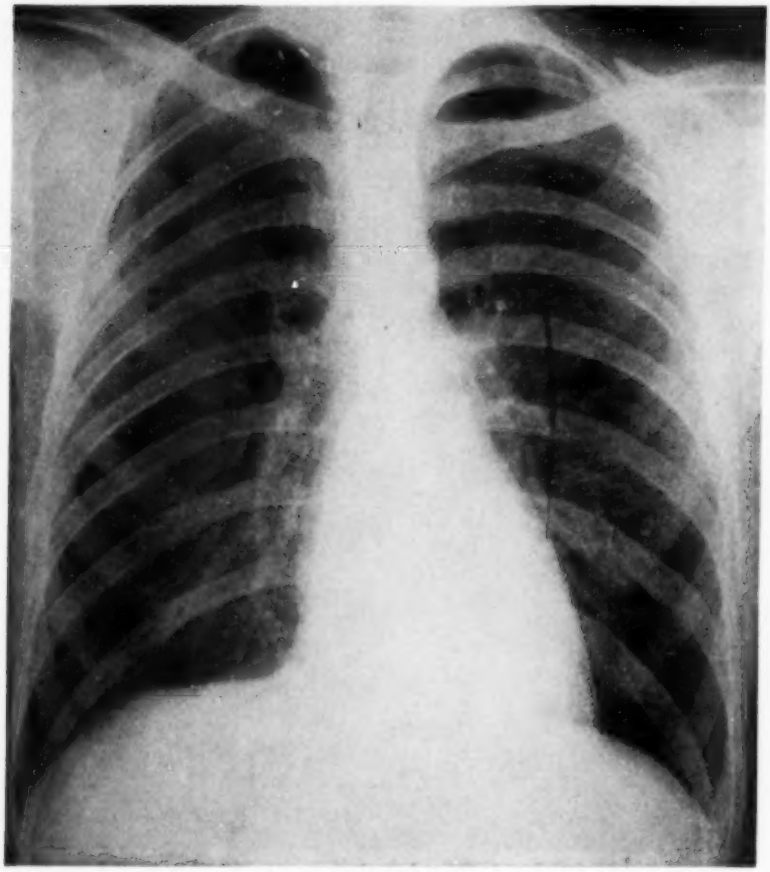

FIG. 4. Chest x-ray of another patient prior to onset of pericarditis.

which varied from 13 to 51 mm. (Wintrobe). Sixteen cases showed an elevation of their white counts above 10,000; the range was from 11,300 to 21,000. It must be remembered that five cases were not seen early. Pericardial fluid was obtained by aspiration and examined in four cases. This showed the fluid to be an exudate with a specific gravity of 1.019 to 1.023;

it contained many cells, which were 80 to 95 per cent lymphocytes; the total protein content varied from 4.5 to 6.0 gm. per cent. Cultures and smears were negative. The pericardial fluid may be bloody.[5] Pericardial biopsy was obtained in one case and showed nonspecific inflammatory changes.

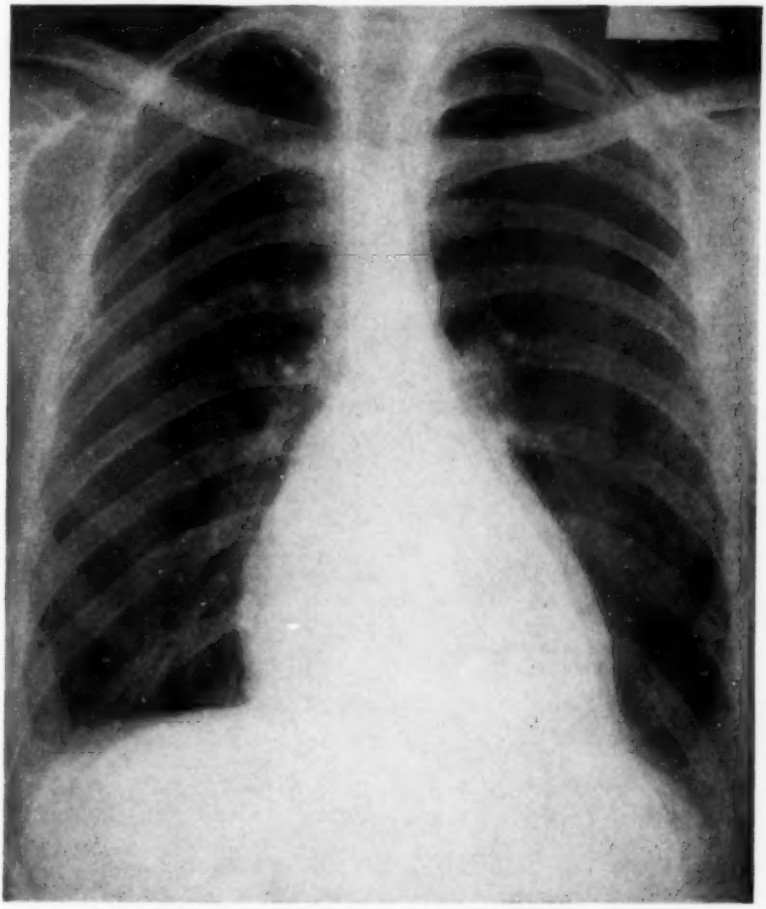

FIG. 5. Same patient showing pericardial and bilateral pleural effusions.

Figure 7 is a low power view showing a thickened pericardium with an infiltration of small inflammatory cells in the deeper layers. Figure 8 is a high power view showing hemorrhage in the right half and leukocytic infiltration in the left half. Figure 9 is another high power view showing collagen fibers in the lower right corner and leukocytic infiltration in the

center. There is no evidence of tubercle formation, and cultures of this tissue were negative.

The electrocardiogram is a valuable diagnostic aid, and has been adequately reviewed in previous reports.[2, 4, 8-10] As Carmichael has pointed out,[4] the electrocardiographic pattern observed depends upon several factors, in-

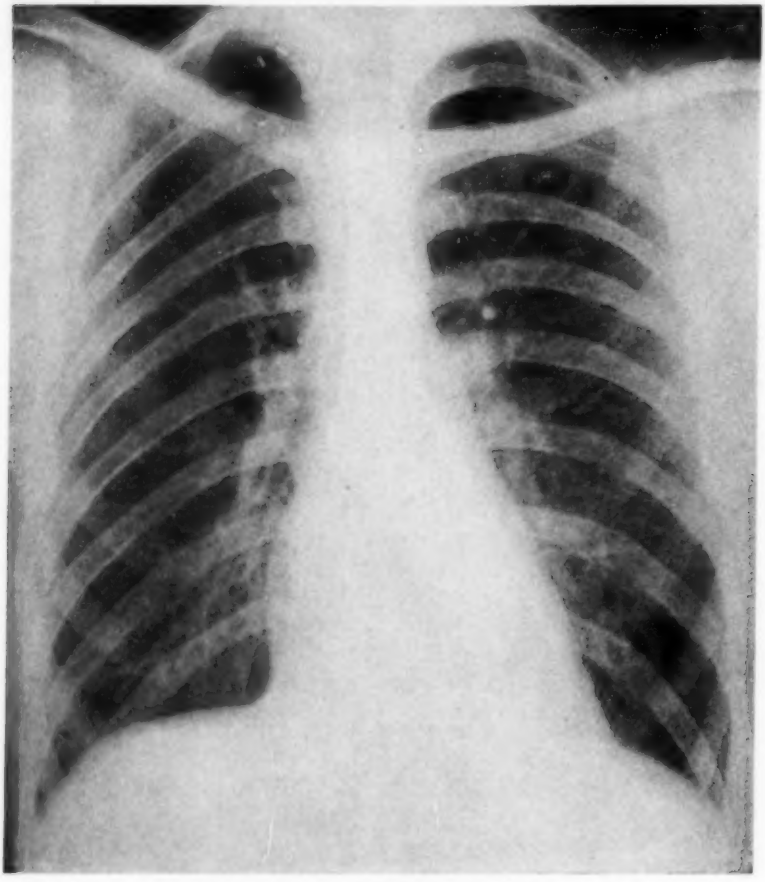

FIG. 6. Same patient three days later.

cluding the phase of the pericarditis, the degree of subepicardial damage, the amount of pericardial effusion, and the adequacy of the electrocardiographic exploration. Unquestionable cases have been reported which showed no electrocardiographic changes[4]; this occurred in one of our cases. Normal or only slightly flattened T waves and minor RST deviation have been re-

FIG. 7. Microscopic section obtained by biopsy showing thickened pericardium.

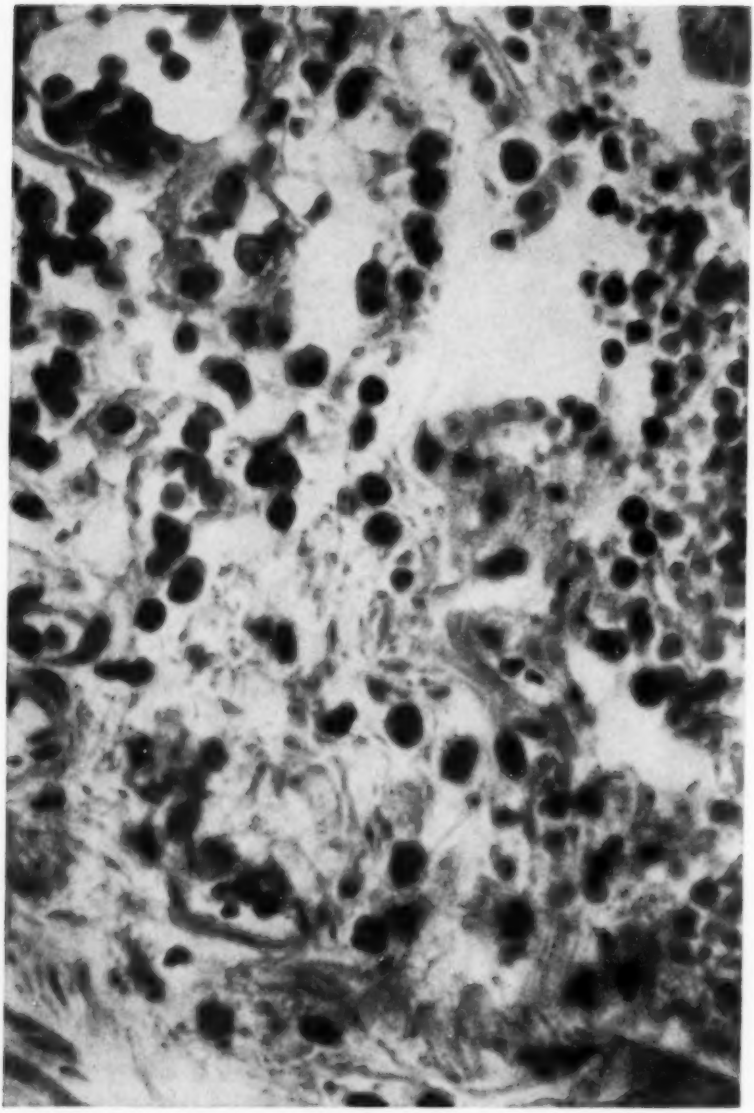

FIG. 8. Higher power of another section from same patient showing hemorrhage and leukocytic infiltration.

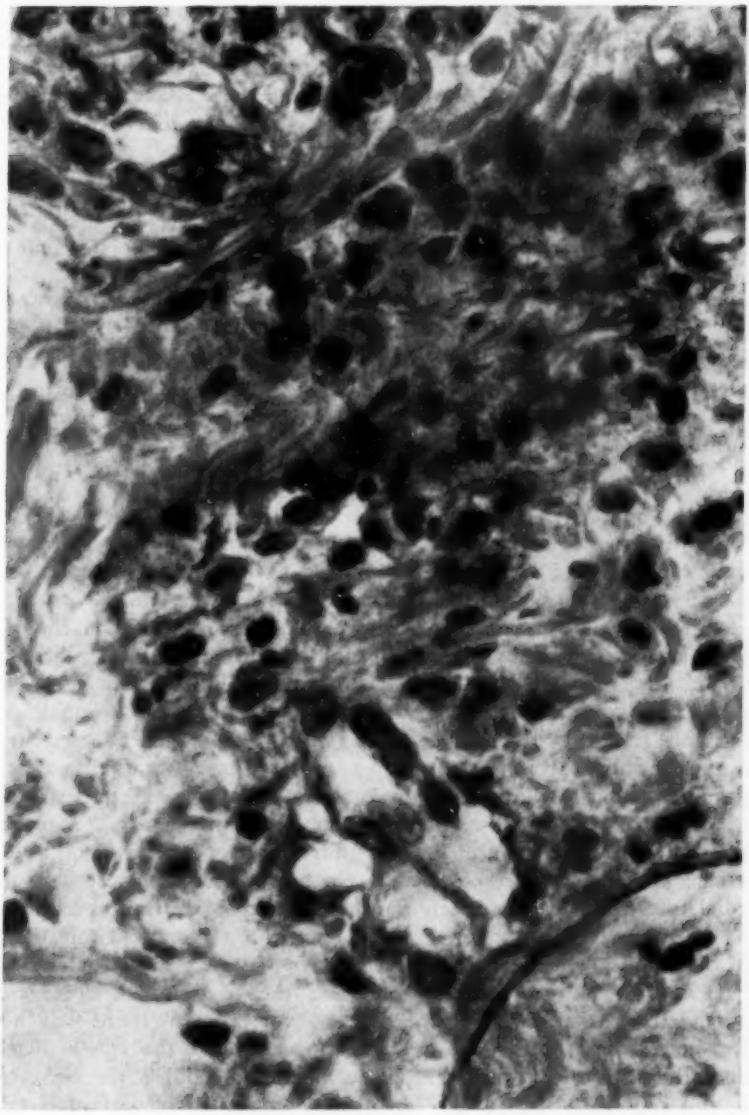

FIG. 9. Another high power section showing collagen fibers within the arc and hemorrhagic infiltration.

ported in many cases, and were found in seven of ours. The characteristic changes are widespread elevation of the ST segment, which may be evanescent, followed by T wave inversion. All but one of our patients had tracings that were within normal limits on discharge, but persistent abnormalities have been reported.[4] Abnormal tracings may be obtained for a few days to three months, but the average duration is about four weeks.

Course and Prognosis

The prognosis is excellent, with complete recovery. The course is quite variable. The duration of our cases was from a few days to four months, the average being three to four weeks. Recurrences are common and are seen in about 30 per cent.[2] Some reports show as many as four recurrences,[4] some occurring years after the initial illness. One of our patients was seen with two typical attacks, and his history indicated that he had had eight similar episodes, but he was not under our observation during any of the preceding attacks. Recurrences tend to be of briefer duration and of a milder nature than the original attack.

Differential Diagnosis

The differential diagnosis is very important, and includes other conditions causing chest pain and a friction rub. Of greatest importance is the differentiation of this syndrome from that of acute myocardial infarction. One implies a good prognosis with complete recovery, while the other implies a serious disease with high mortality and morbidity rates, economic loss and, too frequently, a life of total or semi-invalidism. Another reason for establishing an accurate diagnosis is that today myocardial infarction is commonly treated with anticoagulants, which should not be used in the treatment of acute pericarditis. Pain aggravated by respiration is very uncommon in myocardial infarction but is almost always present in pericarditis. Although shock and circulatory collapse are frequently noted in myocardial infarction, they are infrequent in pericarditis but may occur. Drop in blood pressure and the presence of a gallop rhythm are commonly seen in myocardial infarction, but are rarely if ever encountered in acute pericarditis.[2] The early appearance of a pericardial friction rub, especially within the first 24 hours, and its persistence for several days or weeks, are strong evidence of pericarditis. In myocardial infarction the friction rub appears late (usually the second or third day), rarely ever lasts for more than a few days, and rarely recurs once it has disappeared. If the rub is detected before there are electrocardiographic changes, the odds favor pericarditis over infarction by 100 to 1. The demonstration of pleural involvement and the early appearance of fever and leukocytosis aid in the recognition of pericarditis. Fever and leukocytosis usually attain their maximum on the second to the fourth day in myocardial infarction, whereas they are commonly maximal at the onset in acute pericarditis. Early and adequate

electrocardiography is of the greatest help. The main differential points from myocardial infarction are that in pericarditis one finds: (1) normal QRS complexes; (2) elevated ST segments without reciprocal depression in leads from the opposite wall; (3) the T wave does not invert until the ST returns to the isoelectric line; (4) the inversion tends to be less marked and is deepest in the leads that showed the greatest ST elevation; (5) the changes are usually widespread and appear in multiple leads, as the process is often circumferential; (6) the evolution is more rapid, being measured in days or weeks instead of in weeks or months; and (7) usually the tracing returns to normal.

Acute rheumatic pericarditis may appear before other clinical signs of rheumatic fever, but endocarditis ultimately appears, making the diagnosis obvious. A tuberculous etiology can be identified by the more severe systemic reaction, the prolonged course, the signs of tuberculosis elsewhere, and the positive Mantoux skin test.

Other causes of acute chest pain, such as dissecting aneurysm, angina, hiatus hernia, spontaneous pneumothorax, mediastinal emphysema, acute pleurisy, pulmonary infarction, etc., seldom cause difficulty after complete physical and laboratory examination.

Treatment

Treatment is symptomatic. Many people think that the disease is of viral origin, and it was hoped that some of our broad spectrum antibiotics, particularly aureomycin,[11] would prove effective. We have not been impressed with their efficacy. We have tried practically all of the antibiotics and have found them all ineffective. Our experience has failed to show that any drug appreciably alters the usual course. It must be appreciated that it is extremely difficult to evaluate any therapeutic agent in any disease which pursues such a benign, self-limited course as this one.

There is no indication for the use of anticoagulants. In fact, fatalities have been reported with their use for benign pericarditis.[12]

Summary

The clinical and laboratory features of 28 cases of acute benign pericarditis have been presented. The importance of an accurate diagnosis has been stressed. The value of the pleuritic-type pain, the early appearance of the pericardial friction rub, and adequate electrocardiographic exploration have been emphasized in the differential diagnosis. Treatment is symptomatic and should not include the use of anticoagulants.

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A REVIEW OF THE CURRENT STATUS OF THE CHEMOTHERAPY OF TUBERCULOSIS*

By WILLIAM B. TUCKER, M.D., *Minneapolis, Minnesota*

No drug having been thus far found in the treatment of tuberculosis which kills all tubercle bacilli, the objectives of drug treatment in this disease still fall short of the eradication of all infecting organisms. Nevertheless, with greater understanding in recent years of the pathology of the disease, made possible largely by advances in thoracic surgery, it is now possible to state our clinical objectives more accurately.

It has been found [1] that in pulmonary tuberculosis treated effectively with drugs for adequate periods there is little remaining reversible disease (lobular pneumonitis and tubercles without necrosis), and that the principal remaining components are necrotic nodules and fibrosis. The necrotic nodules frequently contain large numbers of tubercle bacilli, and usually communicate with bronchi or bronchioles, thus furnishing the anatomic prerequisites for potential relapse and dissemination.

The objective in the drug treatment of pulmonary tuberculosis is to achieve as much resolution of the reversible components of the disease as possible; the solution of the problem of the residual necrosis and fibrosis must lie in other directions as long as living tubercle bacilli persist in these areas. It is the purpose of this presentation to review the factors of drug therapy which permit maximal achievement of this limited objective with minimal disadvantage. Factors involved consist of choice of drug, combination of drugs, daily dosage, frequency of administration, duration of therapy, and alteration of drug treatment when studies indicate that only partial success is being achieved.

Evaluation of drug therapy in tuberculosis involves measurements of therapeutic efficacy, such as x-ray improvement, disappearance of tubercle bacilli from sputum and gastric contents, avoidance of relapse, and survival, and measurements of the two principal disadvantages, toxicity and the emergence of organisms resistant to the particular drug or drugs employed. No evaluation is complete without taking these separate factors into account, although it is not possible to give a weighting factor to each with precision.

In the treatment of pulmonary tuberculosis it has been established that streptomycin unquestionably leads to results superior to those of other forms of therapy without streptomycin.[2] Table 1 gives in summary form the results of one coöperating group's investigations as to relative merits of

* From the Symposium on Tuberculosis presented at the Thirty-Fourth Annual Session of the American College of Physicians, Atlantic City, New Jersey, April 15, 1953.

From the Tuberculosis Service, Veterans Administration Hospital, and the Department of Medicine, University of Minnesota Medical School, Minneapolis, Minnesota.

different drug regimens employing streptomycin with respect to efficacy, toxicity and drug-resistance.[3]

It will be seen that, employing streptomycin alone in doses administered daily for four months, there is good therapeutic efficacy but a uniformly high rate of drug-resistance, whether the daily dose be 2.0 gm., 1.0 gm. or 0.5 gm., the only difference being diminishing incidence of toxicity with reduction in dose. The table also indicates that shortening the duration of daily streptomycin therapy, while it results in less toxicity and less drug-resistance, also results in less clinical benefit. When streptomycin is given less frequently, however, at the rate of 1 gm. twice a week, good efficacy is retained, with low degrees of toxicity and drug-resistance.

The hope raised in 1948—that the hydrogenated derivative of streptomycin, dihydrostreptomycin, might result in less toxicity than its parent

TABLE I

General Summary of Effectiveness, Toxicity and Streptomycin-Resistance of Drug Regimens Employed in Treatment of Pulmonary Tuberculosis

Drug Regimen	Duration	Therapeutic Efficacy	Toxicity	Streptomycin Resistance
2 gm. SM*/d.	4 mos.	Good	High	High
1 gm. SM/d.	4 mos.	Good	Medium	High
½ gm. SM/d.	4 mos.	Good	Low	High
1 gm. SM/d.	1½ mos.	Fair	Low	Low
½ gm. SM/d.	1½ mos.	Low	Very low	Low
2 gm. DHSM†/d.	1½ mos.	Fair	Low	Low
1 gm. SM 2x/wk.	4 mos.	Good	Low	Low
1 gm. SM/d. } 1 gm. DHSM/d. }	3–4 mos. 3–4 mos.	Equivalent	SM: more vest. tox. DHSM: more aud. tox.	Equivalent
1 gm. SM/d. +12 gm. PAS‡/d.	4 mos.	Good	Medium	Low
1 gm. SM 2x/wk. +12 gm. PAS/d.	4 mos.	Good	Very low	Very low
1 gm. SM/d. +12 gm. PAS/d. } 1 gm. SM 2x/wk. +12 gm. PAS/d. }	8+ mos.	Excellent	Increase with duration	

* SM—streptomycin.
† DHSM—dihydrostreptomycin.
‡ PAS—para-aminosalicylic acid.

substance—proved unwarranted, for it became apparent that, while less vestibular toxicity occurs with daily dihydrostreptomycin than with daily streptomycin, there is more auditory toxicity. A recent coöperative study of this problem, conducted with meticulous controls, has confirmed the earlier observation and has indicated that, especially when these drugs are administered daily for more than four months, the impairment of auditory function is a serious disadvantage in an appreciable number of patients with dihydrostreptomycin therapy.[4] The incidence of auditory toxicity with the more widely employed twice-a-week administration of dihydrostreptomycin has not been similarly determined.

Table 1, in the lower portion, indicates that when streptomycin is administered concurrently with para-aminosalicylic acid (PAS) there is defi-

nitely less drug-resistance than without that concurrent administration, and that the combination of streptomycin administration twice a week and daily PAS retains satisfactory therapeutic effects with very low toxicity and streptomycin-resistance. With these disadvantages held to reasonably low figures, for the first time it was possible to study the effects of truly prolonged drug treatment, and the last lines of the table indicate that the best results so far obtained have been with this type of drug therapy.

Figure 1 illustrates the percentage of patients treated with streptomycin and PAS who exhibited marked or moderate roentgenographic improvement with varying durations of therapy. When drug treatment is stopped at four months it is seen that there is less improvement one year after the start of therapy than when treatment is continued for nearly a year. Figure 2

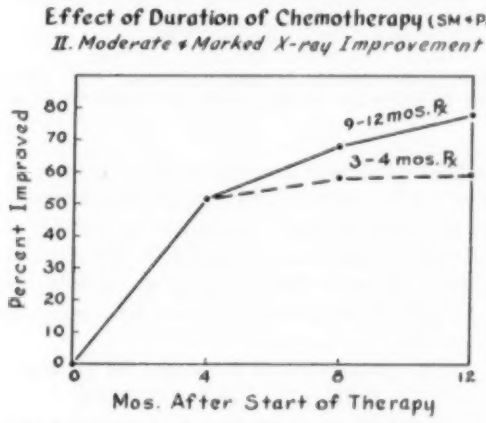

FIG. 1. The effect of the duration of streptomycin and PAS therapy in pulmonary tuberculosis: incidence of moderate and marked roentgenographic improvement at intervals after the start of therapy.

illustrates the same relative picture for conversion of the sputum by culture. It should be mentioned that these data are for cases treated on three different streptomycin and PAS regimens: 1.0 gm. streptomycin a day, 0.5 gm. daily, and 1.0 gm. twice a week, with 12 gm. PAS daily in each instance; and that it has been clearly established [8] that the therapeutic efficacy of these three regimens is the same. The results here illustrated are for "original treatment" cases only, that is, patients who have had no prior drug therapy of any kind for their tuberculosis.

When there has been prior streptomycin therapy which has failed in the control of the disease, re-treatment with streptomycin and PAS is less effective than in "original treatment" patients, even though in vitro tests indicate that organisms from such patients are sensitive to 10 micrograms of streptomycin per milliliter. Figure 3 gives the relative results for moderate

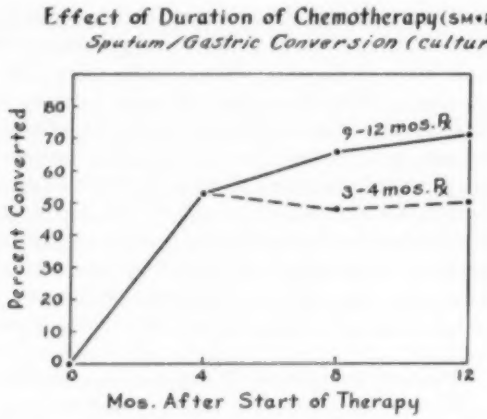

FIG. 2. The effect of the duration of streptomycin and PAS therapy in pulmonary tuberculosis: incidence of sputum or gastric conversion by culture at intervals after the start of therapy.

or marked roentgenographic improvement for three groups of patients: (1) "original treatment"; (2) re-treatment "streptomycin-sensitive," and (3) re-treatment "streptomycin-resistant" cases; and indicates that, roughly proportional to the amount of previous streptomycin therapy and the degree of drug-resistance associated with that therapy, the results are increasingly less satisfactory. Figure 4 illustrates the same differences for sputum con-

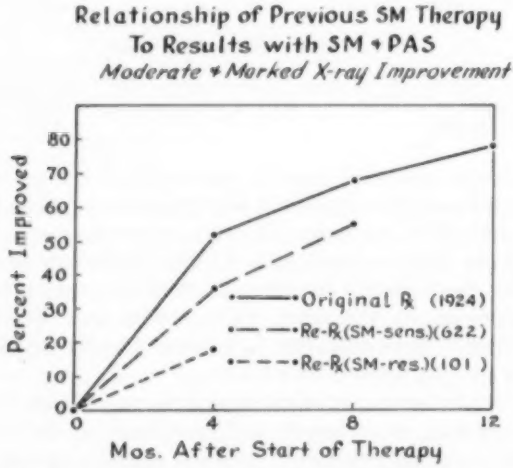

FIG. 3. The effects of previous streptomycin therapy upon the results of the treatment of pulmonary tuberculosis with streptomycin and PAS: incidence of moderate and marked roentgenographic improvement, according to prior therapy and streptomycin-resistance.

version by culture. It is probable that differences in characteristics defining these cases, such as stage of the disease, in part account for these differences.

In spite of such observations it has been shown that when some degree of streptomycin-resistance is present following previous therapy, some continued benefit is to be derived from continued streptomycin therapy, provided that degree, established in vitro, does not exceed complete resistance to 100 mcgm./ml. Figure 5 illustrates the results of treatment with PAS alone and with streptomycin and PAS, with respect to x-ray improvement, in a controlled study of such individuals, indicating that when there is complete resistance to 100 mcgm./ml. of streptomycin the combination of streptomycin and PAS therapy is approximately the same as that with PAS alone.

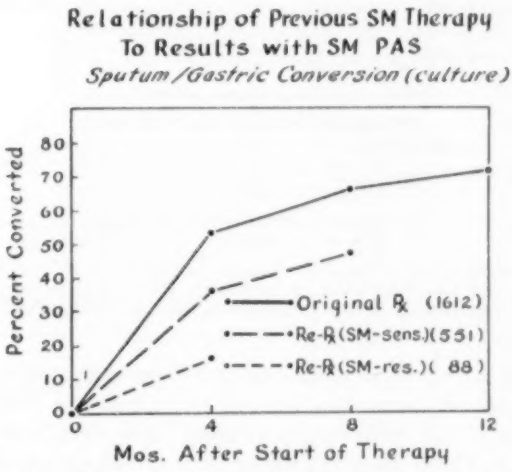

FIG. 4. The effects of previous streptomycin therapy upon the results of the treatment of pulmonary tuberculosis with streptomycin and PAS: incidence of sputum or gastric conversion by culture, according to prior therapy and streptomycin-resistance.

The incidence of toxicity to the eighth cranial nerve is the most important manifestation with prolonged administration of streptomycin or dihydrostreptomycin (with or without PAS) on the dosage regimens now most commonly employed. With respect to vestibular toxicity, when therapy is continued approximately eight months there is significant impairment in approximately 10 per cent of patients treated with 1.0 gm. streptomycin daily, in approximately 5 per cent treated with 1.0 gm. dihydrostreptomycin daily, 3 per cent treated with 1.0 gm. streptomycin twice weekly, and in only 1 or 2 per cent treated with 0.5 gm. streptomycin daily.[5] On the other hand, the incidence of auditory impairment of significant degree is clearly greater with daily dihydrostreptomycin than with daily streptomycin. Because each of these drugs appears to offer certain advantages, it has recently been

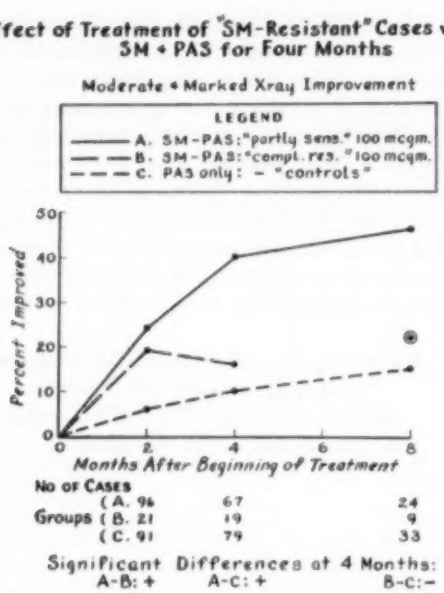

FIG. 5. Comparison of effects of re-treatment of pulmonary tuberculosis with streptomycin and PAS, and with PAS alone, in individuals with organisms resistant to different concentrations of streptomycin in vitro: incidence of moderate and marked roentgenographic improvement.

proposed [6] that a 1 gm. dose, consisting of 0.5 gm. streptomycin and 0.5 gm. dihydrostreptomycin, be employed in place of 1.0 gm. of either drug alone. Full evaluation of this interesting possibility has not yet been made.

Reference has been made to relative rates of emergence of resistance to streptomycin. Some data on this phenomenon related to drug regimen are given in tables 2 and 3.[7] These data can be summarized as follows: (1) Rates are much higher on regimens without PAS than with PAS; (2) rates are higher with daily than with twice-a-week administration of streptomycin; (3) rates are lowest, in "original treatment" cases, with the regimen of twice-a-week streptomycin and daily PAS, up to four months of treatment,

TABLE II

Incidence of Resistance to Streptomycin among Patients Treated on Various Regimens (Per Cent of Cases with Positive Cultures Observed at 4 Months)

	Resistant to 10 mcgm./ml.	Resistant to 100 mcgm./ml.
Daily SM for 4 mos.	80	50
Daily SM for 3 mos.	70	40
Daily SM for 42 days	40	25
Twice a week SM for 4 mos.	55	35
Daily SM, daily PAS, for 4 mos.	25	15
2x/wk. SM, daily PAS, for 4 mos.	15	5

but with therapy prolonged to eight months this advantage is at least partly lost; (4) rates are higher in "re-treatment streptomycin-sensitive" cases than in "original treatment streptomycin-sensitive" cases; and (5) the rate of emergence of resistance of organisms resistant to 100 mcgm. per ml. of streptomycin is approximately 60 per cent of that of organisms resistant to 10 mcgm./ml.

Inadequate attention has perhaps been paid to the rate of emergence of organisms resistant to PAS. A recent study has appeared to indicate that

TABLE III

Incidence of Resistance to Streptomycin in Different Concentrations According to Type and Duration of Therapy

	Streptomycin-Resistance*		
	PR+R	PR	R
	10 mcgm./ml.	100 mcgm./ml.	
	(Per Cent)		
A. Original Treatment Cases			
Four months therapy			
Daily SM, daily PAS	25	15	6
Twice a week SM, daily PAS	15	4	2
Eight months therapy			
Daily SM, daily PAS	35	20	12
Twice a week SM, daily PAS	35	20	12
B. Re-treatment "SM-sens." Cases			
Four months therapy			
Daily SM, daily PAS	40	15	6
Twice a week SM, daily PAS	35	10	4
Eight months therapy			
Daily SM, daily PAS	55	40	25
Twice a week SM, daily PAS	40	—	—
C. Re-treatment "SM-res." cases			
Four months therapy (da. SM–PAS)	70	50	30
Eight months therapy (da. SM–PAS)	80	—	—

* PR—partially resistant: less growth than on control tube.
R—completely resistant: growth equal to that on control.

continuous administration of PAS is important in avoiding therapeutic failures, as is also the retention of PAS-sensitivity [8]; and it does not appear to be indicated to employ PAS alone for extended periods of time, to "reserve" streptomycin-sensitivity. Data in table 4 indicate that prior treatment with streptomycin, associated with some loss of streptomycin-sensitivity, increases the rate of emergence of PAS resistance. Administration of PAS twice a week unfortunately has been found to be less effective than daily administration of PAS, with twice-a-week streptomycin.[9]

TABLE IV

Incidence of Resistance to PAS

Regimen	Per Cent Cases Resistant on			
	4 Months Therapy		8 Months Therapy	
	to 10 mcgm./ml.	to 100 mcgm./ml.	to 10 mcgm./ml.	to 100 mcgm./ml.
A. Original Treatment Cases				
Daily SM, daily PAS	10	4	25	13
Twice a week SM, daily PAS	15	5	25	13
B. Re-treatment "SM-sens." Cases				
Daily SM, daily PAS	40	15	55	40
Twice a week SM, daily PAS	35	10	35(?)	—
C. Re-treatment "SM-res." Cases				
Daily SM, daily PAS	70	50	80	

Rates of emergence of tubercle bacilli resistant to an antituberculous drug appear to be especially related to the size of the cavitary component. A study in 1949 indicated (figure 6) that the larger the cavitary component the higher the rate of emergence of streptomycin-resistant organisms, with identical drug treatment given to all groups.[10]

Such data as these suggest that results with drug treatment will vary with the composition of the cases under therapy. Among patients treated with prolonged courses of streptomycin and PAS, for example, it has been

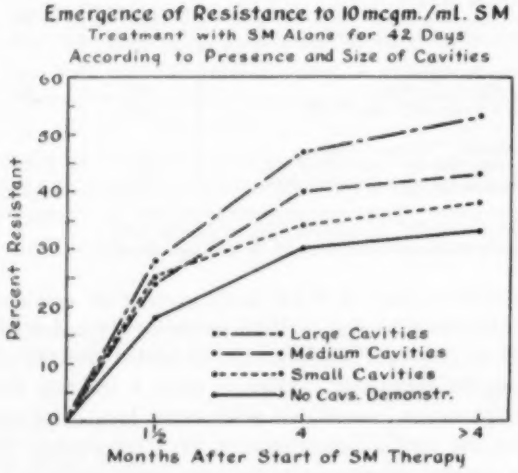

FIG. 6. Rates of emergence of streptomycin resistance (to 10 mcgm./ml.). According to size of cavitary component, treatment with streptomycin alone for 42 days.

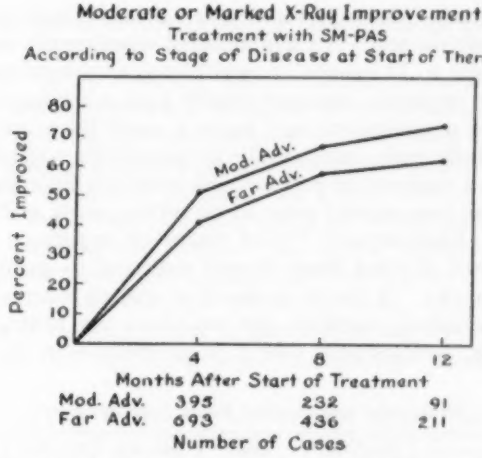

FIG. 7. Rates of roentgenographic improvement of moderate and marked degree in pulmonary tuberculosis treated with streptomycin and PAS, according to stage of disease at start of therapy.

ascertained that there is more roentgenographic improvement (figure 7) and more sputum conversion by culture (figure 8) in moderately advanced than in far advanced disease.[11] Such observations are equally true for the three variations in streptomycin dosage studied, with PAS: 1.0 gm. a day, 0.5 gm. a day, and 1.0 gm. twice a week.

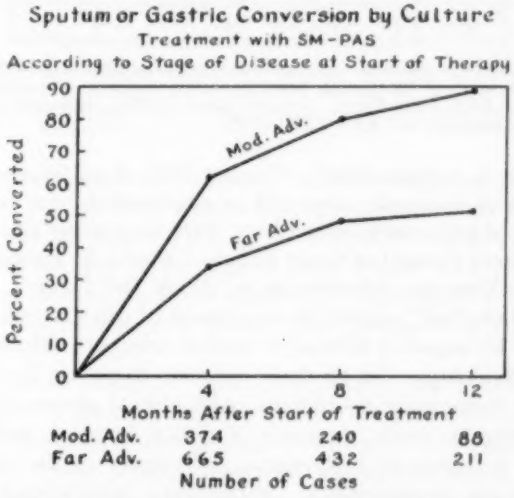

FIG. 8. Rates of sputum or gastric conversion by culture in pulmonary tuberculosis treated with streptomycin and PAS, according to stage of disease at start of therapy.

From these studies the interpretation is warranted that a regimen consisting of streptomycin and PAS administered concurrently over prolonged periods (up to eight to 12 months or more) leads to clinical results superior to those of other regimens; and particularly with a regimen involving the administration of streptomycin only twice a week there are toxicity and drug-resistance sufficiently infrequently to permit the application of such therapy in the vast majority of patients with relatively little disadvantage.

This much had been learned prior to the advent, early in 1952, of a new drug, isoniazid. Early reports [12, 13] of treatment in patients largely representing the failures of other drug therapy indicated its great promise and relatively low toxicity. A test of isoniazid in miliary tuberculosis, in many respects the tuberculous condition *par excellence* for testing a new antituberculous drug, demonstrated that it is as effective in the treatment of

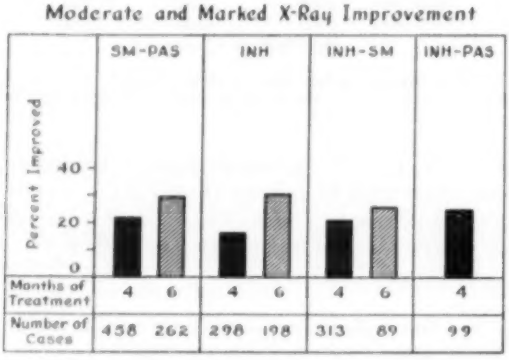

FIG. 9. Incidence of moderate and marked roentgenographic improvement at four and six months after start of therapy in patients with pulmonary tuberculosis treated with streptomycin and PAS (SM-PAS), isoniazid alone (INH), isoniazid and streptomycin (INH-SM), and isoniazid and PAS (INH-PAS).

tuberculosis as is streptomycin.[14] During 1952 three large-scale trials for the evaluation of isoniazid, alone and in combination with other drugs, in the treatment of pulmonary tuberculosis, have been under way: those of the Medical Research Council of Great Britain,[15] the U. S. Public Health Service [16] and the Veterans Administration, Army and Navy.[3] All have employed the "controlled" method of assignment of cases to one drug regimen or another by an impartial method of random selection, differing in the finer points of methodology. In all three instances there has been participation by groups of coöperating institutions, with mutual agreement on the principles governing the study, a pooling of clinical material, and a willingness to surrender a degree of professional sovereignty in the interests of the objectives of the investigations. Preliminary reports thus far available have indicated in each instance that isoniazid is as effective as is strepto-

mycin in the treatment of tuberculosis, at least in the early months of treatment.

In the study of the Veterans Administration, Army and Navy,[8] therapeutic efficacy has been shown to be approximately equivalent, as measured by roentgenographic improvement and sputum conversion by culture, among patients treated on the following regimens: isoniazid alone, in doses of either 150 mg. or 300 mg. a day; streptomycin, 1 gm. twice a week, and PAS, 12 gm. a day; 300 mg. isoniazid daily and 1 gm. streptomycin twice a week; and 300 mg. isoniazid and 12 gm. PAS daily. Figure 9 illustrates the results for x-ray improvement, and figure 10 for sputum conversion by culture. Figures from this study for relapse, however, indicate that with four to five months of treatment there is more worsening after initial improvement on the regimens employing isoniazid alone than on the others. Data

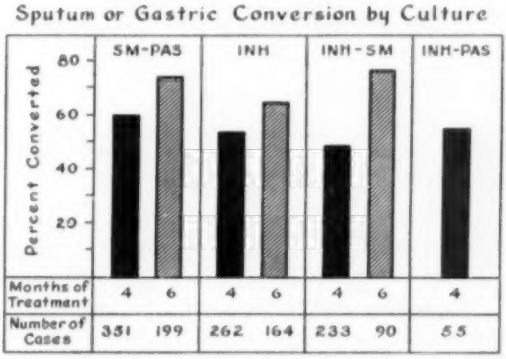

FIG. 10. Incidence of sputum or gastric conversion by culture at four and six months after start of therapy in patients with pulmonary tuberculosis treated with streptomycin and PAS (SM-PAS), isoniazid alone (INH), isoniazid and streptomycin (INH-SM), and isoniazid and PAS (INH-PAS).

from the Public Health Service study indicate somewhat similar trends. For example, at the end of 28 weeks of treatment 47 per cent of the patients treated with streptomycin and PAS, 54 per cent of those treated with streptomycin and isoniazid, and 51 per cent of those treated with isoniazid alone, demonstrated at least moderate roentgenologic improvement,[16c] and the percentages for sputum conversion for the three groups were 73, 89 and 58, respectively.[16d]

The picture with respect to isoniazid-resistance has been only partially clarified to date, in contrast to that of streptomycin-resistance. Among sputum-positive patients with organisms sensitive to 10 mcgm./ml. of streptomycin in vitro (both original treatment and re-treatment), the rates of emergence of bacilli resistant to 1 mcgm./ml. isoniazid on three different regimens are given in figure 11. Rates for sputum-positive patients with

bacilli showing 1 plus or more growth on the 5 mcgm./ml. tube are given in figure 12, there being the same relative position of the curves in the two figures, but at a level approximately one third lower in the case of resistance to the higher concentration of the drug. If similar data for "streptomycin-resistant" cases are gathered, all rates are correspondingly higher, probably related to the more chronic and cavitary status of the disease in these patients.

From these data it is apparent that lower rates of isoniazid-resistance are obtained with treatment with isoniazid in combination with either streptomycin or PAS. Table 5 also indicates that, with respect to delaying the rate of the emergence of streptomycin-resistance, either PAS or isoniazid is

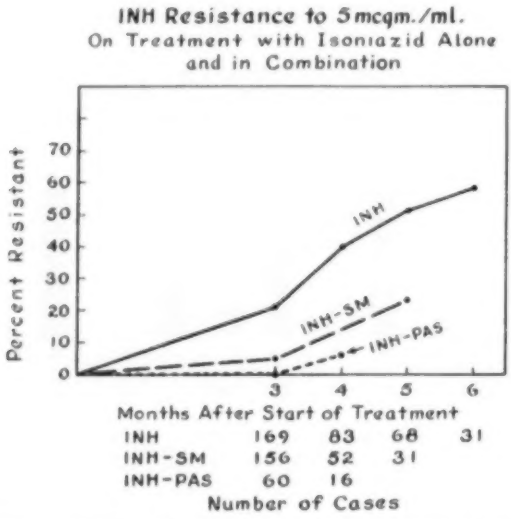

FIG. 11. Rates of emergence of resistance in vitro to 1 mcgm./ml. of isoniazid in patients with pulmonary tuberculosis treated with isoniazid alone (INH), isoniazid and streptomycin (INH-SM), and isoniazid and PAS (INH-PAS).

approximately equally effective. Incidence of drug resistance may be expressed either as the per cent of a total group treated or as the per cent of individuals with positive cultures, and comparisons between therapeutic groups will depend upon the sputum conversion rates. Thus, for growth in the 5 mcgm./ml. tube, the Public Health Service study shows that after 28 weeks of treatment with isoniazid alone the incidence of isoniazid-resistance is 52 per cent in cases with positive cultures, but only 25 per cent for the entire group; and for treatment with streptomycin and isoniazid the corresponding rates are 58 and 14 per cent, respectively.[16d] It would appear that valuable information is to be derived from both methods of reporting.

The clinical significance of isoniazid-resistance is not clear at present and

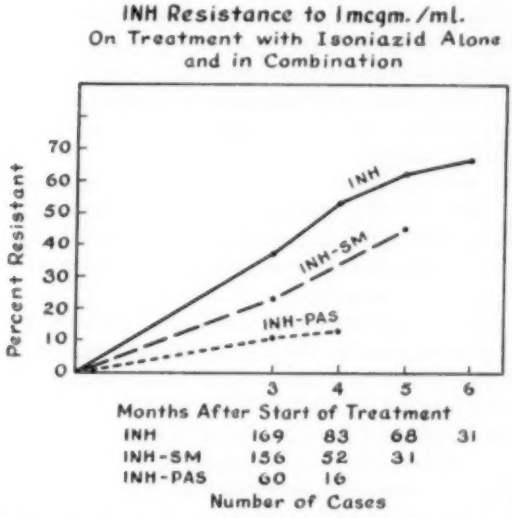

FIG. 12. Rates of emergence of resistance in vitro to 5 mcgm./ml. of isoniazid (1+ or more growth) in patients with pulmonary tuberculosis treated with isoniazid alone (INH), isoniazid and streptomycin (INH-SM), and isoniazid and PAS (INH-PAS).

must await further study. Some reports have indicated that there may be diminished virulence of tubercle bacilli from patients treated with isoniazid which are found in vitro to be isoniazid-resistant.[17]

While toxicity to isoniazid does occur, it is relatively low in its incidence, requiring discontinuation of therapy in only approximately 2 to 3 per cent of cases, when administered in daily doses of 2 to 5 mg./kg. body weight (150 to 300 mg./day for average adults).

It is clear from such studies as have been cited that while treatment with streptomycin and PAS, and with isoniazid, has done much to influence the course of clinical tuberculosis, to convert sputum, to aid in the resolution of the reversible component of the disease, and to prolong life, there are

TABLE V

Comparison of PAS and Isoniazid Delaying Emergence of SM-Resistance
(Original and Re-Treatment "SM-Sens." Cases)

	Cases Treated for 3–4 mos. (Per Cent)	Cases Treated for 4–5 mos. (Per Cent)
A. Resistance to 10 mcgm./ml. SM (partial or complete)		
Daily PAS with twice a week SM	23	22
Daily INH* with twice a week SM	16	18
B. Resistance to 100 mcgm./ml. SM (complete)		
Daily PAS with twice a week SM	3	3
Daily INH* with twice a week SM	4	8

* INH—isoniazid (isonicotinic acid hydrazide).

therapeutic failures, with persistence of positive sputum and a certain incidence of relapse. In such cases there nearly always is a relatively high degree of drug-resistance to such antituberculous agents as may have been employed; and when this drug-resistance is found to the most effective agents available, a more serious problem is presented if there is need for further antimicrobial therapy.

Under these circumstances viomycin has been found to be an effective antituberculous agent.[18] Too toxic when administered in doses of 2 to 3 gm. a day, it may with fair safety be administered with the same dose twice a week, with definite antituberculous effect, if less than that of streptomycin or isoniazid in untreated patients.

As it has been demonstrated to be clearly desirable to give no antituberculous drug alone, and as PAS is the drug most commonly administered with streptomycin, the problem of PAS-intolerance, whether due to drug toxicity or allergy, may be a serious one.[19] In these circumstances it has been demonstrated that Terramycin, in doses of 3 to 5 gm. a day, may be given with streptomycin and have approximately the same effect in delaying the emergence of streptomycin-resistance as does PAS.[20]

Discussion

In this brief review there has been no attempt to cover the numerous excellent investigations of antimicrobials in experimental tuberculosis. There has been no reference to the study of treatment of tuberculous conditions other than pulmonary tuberculosis, although limited data from such studies would largely substantiate the observations made. And there has been no effort made to integrate drug therapy with other elements of the treatment of tuberculosis, which obviously are equally important. For example, widely practiced today is the excision of residual necrotic pulmonary nodules, after prolonged chemotherapy, but it has not been established that this practice improves the late results. Studies of such resected tissue demonstrate rather uniformly that tubercle bacilli are present on stained smear, but infrequently grow on culture media or produce disease in guinea pigs. The question of the viability of such organisms has not been entirely clarified, although it is apparent that some fundamental change has occurred in the bacilli, not so much perhaps through a direct action of the antituberculous drug as through physicochemical mechanisms made possible by the effective use of the drug.[21] The question as to whether it may be permissible and in the best interests of the patient to administer prolonged drug therapy on an ambulant or even an out-patient basis naturally arises and deserves careful study, but there should not be an unwarranted adoption of such a plan on a therapeutic basis until there has been careful evaluation of such a program.

From many sources it is apparent that the institutional death rate from tuberculosis has been declining rapidly with the wider application of modern

effective chemotherapy. While it is possible to postpone death, the ultimate goal of eradication of tuberculous infection has thus far escaped us. Short of that goal, a considerable degree of partial success is within the grasp of the clinician of 1953, if the considerations discussed are kept in mind.

Summary

From a number of different coöperative studies, carefully conducted with controls assigned by randomization, it has been possible to establish in the last few years the superiority of certain variables in the chemotherapy of tuberculosis. A combination of 1 gm. of streptomycin administered twice a week with 12 gm. daily of PAS, for periods up to one year, has been found to result in a high degree of therapeutic efficacy and relatively little toxicity and drug-resistance. Isoniazid in combination with streptomycin or with PAS also appears to be effective, although the recency of its advent has not yet permitted as complete evaluation as with streptomycin and PAS.

Results of chemotherapy in general are less satisfactory when there has been prior chemotherapy than in "original treatment" patients, and this is in part related to drug resistance. When partial streptomycin-resistance has developed as the result of prior streptomycin therapy, some benefit is nevertheless to be derived from continued streptomycin therapy unless that resistance is found to be as high as complete resistance to 100 mcgm./ml. The availability of isoniazid, as a second effective drug, improves the clinical outlook in these patients.

When drug resistance to both streptomycin and isoniazid has developed, viomycin is found to be an effective antituberculous agent, though probably of more limited efficacy than streptomycin or isoniazid.

It is desirable always to give combined therapy with more than one antituberculous drug, and PAS appears to be the preferred drug to give with either streptomycin or isoniazid. When intolerance to PAS exists, Terramycin may be employed as a substitute.

Effective chemotherapy in tuberculosis results in the resolution of the reversible components of the disease in a high percentage of cases, leaving residual fibrosis and necrosis. The best clinical management of such residual tuberculous disease, in association with prolonged effective chemotherapy, has not been determined with precision.

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PRIMARY AND SECONDARY GOUT*

By ALEXANDER B. GUTMAN, M.D., F.A.C.P., *New York, N. Y.*

THERE is now some indication that the clinical syndrome of gout may well comprise several distinct anomalies of purine metabolism.[1] Of these at least one may properly be considered a primary form of gout, the others as secondary to some other disease, usually involving the hematopoietic system.

Primary gout is the common category of the disorder, and is more widespread than is often appreciated. As suspected by Garrod,[2] gout (in its primary form) may be classified as an inborn error of purine metabolism.[3] Recent surveys [4-6] of asymptomatic members of the families of patients with overt gout have revealed so high an incidence of familial asymptomatic hyperuricemia (25 per cent or more) as to make genetic analysis feasible. The underlying metabolic fault appears to be inherited as a single dominant trait, with incomplete penetrance. The transmitting gene clearly is autosomal, not sex-linked; indeed, the incidence of the gouty trait, as indicated by hyperuricemia, appears to be high in female members of gouty families, even though only some 5 per cent of cases of overt gout occur in women.

It has been apparent for some time that there is, normally, a sex difference with respect to purine metabolism—for example, serum urate levels are significantly lower in healthy females than in males. Yü, employing a modification of the Buchanan, Block, Christman method [7] incorporating the use of uricase, arsenophosphotungstic and urea cyanide-carbonate, found the mean serum urate level of 96 normal women to be 4.3 $\pm$1.0 mg. per cent, as compared with 5.3 $\pm$ 1.7 mg. per cent in 91 normal men. This sex difference may be related, in part, to a generally somewhat higher renal urate clearance in normal females,[8-10] as well as to possible divergencies in urate biosynthesis. A similar sex differentiation in respect to serum urate levels obtains also in gouty subjects. In male bearers of the genetic trait, hyperuricemia seldom develops before the age of puberty,[3, 8] but in female carriers ordinarily not until much later in life, and then usually to a lesser degree. The underlying cause of this basic difference in purine metabolism and excretion in the sexes is not known, and the reasons why gout becomes clinically manifest so infrequently in females with hyperuricemia due to the gouty trait are still obscure.

Some information is now available as to the general nature of the metabolic anomaly in primary gout, at least in the approximately 25 per

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From The Department of Medicine, The Mount Sinai Hospital, and the Department of Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y.

cent or more of cases which give evidence of overproduction of urate by habitually excessive urinary excretion of urate on a low purine, restricted protein diet. In two such subjects it has been possible to demonstrate directly, by oral administration of N^{15}-labeled glycine, a threefold increase over the normal in the N^{15}-labeled urate recovered from the urine [11-13] (figure 1). This indicates a corresponding diversion of glycine, a precursor of uric acid, from metabolic pathways leading to formation of urea and other end-products of metabolism to those terminating in uric acid. To judge from the rapid conversion to purine N^{15}, such overproduction of urate does not appear to involve intermediary incorporation of glycine nitrogen into nucleic acids. There is no convincing evidence at present for greatly accelerated breakdown of endogenous nucleic acids in primary gout.

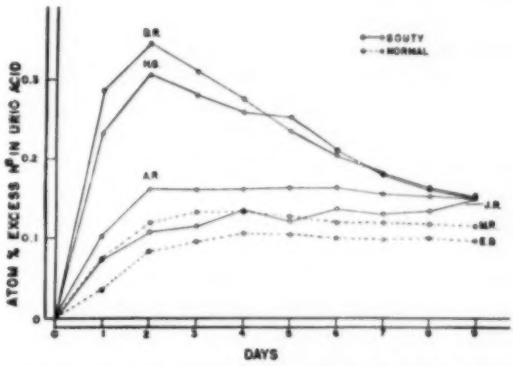

FIG. 1. Rate of incorporation of N^{15}-labeled glycine into uric acid recovered from the urine. D. R. and H. G. are cases of gout habitually excreting excessive amounts of uric acid in the urine; approximately 3 times the normal amount of N^{15} was incorporated into uric acid, with peaks at about the second day. A. R. and J. R. are cases of gout habitually excreting quantities of uric acid within the normal range; the deviation from normal control subjects (M. R. and E. B.) is not significant. (From Benedict et al.[13])

The metabolic divergence in primary gout is more complex than this, however. In three gouty subjects excreting quantities of urate within the normal range, similar isotope technics failed to demonstrate overproduction of urate.[13, 14] Whether these negative results indicate that the same metabolic anomaly may operate intermittently or at an undetectably low rate, or whether they implicate the operation of some other deviation of metabolism, cannot now be determined.

Secondary gout may occur, occasionally, in the course of primary polycythemia,[15-16] secondary polycythemia, myeloid metaplasia,[17] chronic leukemias, Cooley's anemia [18] and other chronic hemolytic anemias in adults, pernicious anemia, and in the malignant lymphomas; it is rarely if ever associated with the hyperuricemia of chronic nephritis or multiple myeloma. The incidence of overt gout is low in these disorders of the bloodforming

organs, and in many instances doubtless represents a chance concurrence with primary gout. There is good reason to suspect, however, that this is not always the case. In polycythemia vera the incidence of typical gouty arthritis associated with hyperuricemia has been reported [15, 16] to be 5 per cent and 9 per cent—too high a figure to be due to chance—with more frequent involvement of females than occurs in primary gout. Moreover, in many instances there is a distinct temporal relationship to treatment: radiation therapy or chemotherapy in the case of polycythemia and the leukemias, liver or vitamin B_{12} therapy in the case of pernicious anemia. Familial occurrence of gout in such subjects is not conspicuous, and genetic transference is not likely.

This form of gout therefore appears to be due not to an inborn error of metabolism, but rather to an acquired acceleration in the degradation of nucleic acids, with liberation into the blood of a plethora of intermediary purines, including the metabolic end-product, uric acid. The most obvious indication of such flooding of the body with purines is the not infrequent occurrence of uremia due to ureteral obstruction by urate crystals following radiation or chemotherapy in leukemia [19, 20] and related disorders. A fourfold increase in the size of the miscible pool of urate has been reported in a case of leukemia.[21]

Direct evidence for this view was obtained by a study made in collaboration with Dr. DeWitt Stetten and his associates.[22] N^{15}-labeled glycine was fed to a patient with marked polycythemia secondary to a congenital heart lesion and latterly associated with recurrent acute gout and extensive tophaceous deposits. Unlike the experience in primary gout, the accumulation of N^{15}-labeled urate in the urine of this subject was slow, reaching a peak at about the tenth day—a finding consistent with the relatively slow turnover of nucleic acids.

Major Pathways of Purine Metabolism in Man

Since the pathogenesis of both primary and secondary gout relates so closely to exaggerations or deviations of the several normal pathways of purine metabolism, further insight into the mechanisms of the disease can best be gained by referring to our present knowledge of the normal metabolic processes. Various aspects of this complex subject are covered in detail in recent reviews by Schlenk,[23] Laskowski [24] and Christman,[25] and in a recent comprehensive symposium on the chemistry and metabolism of nucleic acids.[26]

There are, in general, three major metabolic pathways of purine metabolism to be considered in relation to the over-all problem of gout:

1. Biosynthesis of purines and purine derivatives directly from simple carbon and nitrogen compounds without intermediary incorporation into nucleic acids.

2. Biosynthesis and degradation of "endogenous" nucleic acids.

3. Degradation of ingested (exogenous) preformed nucleoproteins, nucleic acids and purines.

Direct Biosynthesis of Purines: It has been known for some time, through the in vitro experiments of Schuler and Reindel and of Krebs and his associates, that pigeon liver slices can synthesize hypoxanthine rapidly from suitable precursors. More recent investigation by Buchanan and collaborators,[27-29] Greenberg [30, 31] and others, utilizing isotope labeling, has clarified the enzyme reactions involved, disclosing hitherto unsuspected precursors and metabolic pathways of direct purine synthesis, and permitting precise localization of the position in the uric acid molecule of each precursor contribution. The elucidation of these mechanisms is a brilliant achievement in the application of isotopes to biologic problems.

Uric acid can be synthesized in the body directly, without intermediary incorporation into nucleic acids, from glycine, ammonia, a one-carbon compound equivalent to formic acid, and carbon dioxide. The carbon atoms occupying positions 4 and 5 of the uric acid molecule are derived from the

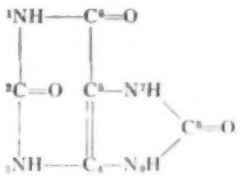

FIG. 2. Numbering of atom positions in uric acid molecule. For relation to precursors in biosynthesis, see text.

carboxyl and methylene carbons, respectively, of glycine (to which serine and threonine are readily converted); the ureide carbons in positions 2 and 8 are derived from "formate"; carbon atom 6 is incorporated by fixation of carbon dioxide; nitrogen 7 is derived from glycine; and the nitrogen atoms in positions 1, 3 and 9 are derived from the general metabolic pool of ammonia nitrogen, in part by way of aspartic acid, glutamic acid and glutamine (figure 2). As Greenberg[30, 31] has shown in in vitro experiments with pigeon liver preparations, the over-all reaction, which involves the intermediate formation of 4-amino-5-imidazolecarboxamide ribotide (figure 3) and the appearance of inosinic acid as the first purine product, may be schematically represented thus:

$$CO_2 + 3\ NH_3 + \text{glycine} + \text{"formate"} + \text{ribose-1-phosphate} \longrightarrow$$

$$\text{4-amino-5-imidazolecarboxamide ribotide} \xrightarrow{+\text{ "formate"}} \text{inosinic acid}$$

$$\xrightarrow{-H_3PO_4} \text{inosine} \xrightarrow{+H_3PO_4} \text{hypoxanthine} + \text{ribose-1-phosphate}.$$

Hypoxanthine is indicated as the final purine product of these reactions, since pigeon liver is devoid of xanthine oxidase, but in mammals hypoxanthine

is readily oxidized by xanthine oxidase to xanthine and then to uric acid.

It is of interest that in the incorporation of "formate" in position 2, citrovorum factor (formyl coenzyme F) acts as a transformylating medium. Homocysteine also participates in incorporation of formate. Vitamin B_{12} plays an important rôle in purine synthesis but the precise nature of its action is still uncertain.

Most of these reactions have been established by in vitro methods, and in vivo experiments in birds and lower mammals, but there is indication that metabolic pathways for biosynthesis of purines without intermediary incorporation into nucleic acids occur also in man. In 1947 Shemin and Rittenberg [32] demonstrated in a normal human subject that the nitrogen of N^{15}-labeled glycine was rapidly incorporated into position 7 of the excreted uric acid. That glycine is a precursor of uric acid in man, and is incorporated, in part, at a rate which would appear to preclude routes involving turnover of nucleic acids, has since been amply confirmed.[11, 13, 14] Evidence that such metabolic pathways of direct biosynthesis of purines play an important rôle in the overproduction of urate characterizing some subjects with primary gout has already been cited.

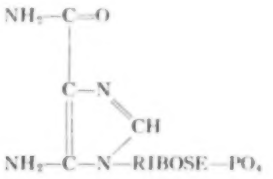

FIG. 3. Formula of 4-amino-5-imidazolecarboxamide ribotide, intermediate in direct biosynthesis of purines.

Biosynthesis and Degradation of "Endogenous" Nucleic Acids: Until the direct metabolic routes for purine biosynthesis were established comparatively recently, uric acid in man was generally believed to derive almost wholly from the breakdown of "endogenous" and "exogenous" nucleic acids. These universally distributed, essential cellular constituents are macromolecular polymers of nucleotides. They are divisible into two main groups: the pentose nucleic acids (PNA), which on alkaline hydrolysis yield the ribose nucleotides of adenine, guanine, cytosine and uracil, each apparently in two isomeric forms; and the desoxypentose nucleic acids (DNA), chromosomal constituents which on hydrolysis yield the corresponding 2-desoxyribose nucleotides of adenine, guanine, thymine, cytosine and, in higher forms in small amount, 5-methylcytosine. These components formerly were thought to occur in nucleic acids as tetranucleotide unit polymers containing the four principal purine and pyrimidine bases in regular repetitive sequence. It is now clear that these bases are not distributed in equimolar proportions throughout the nucleic acid molecule but occur in diverse patterns, individually characterized by cores disproportionately rich in purine nucleotides

and (at least in the case of PNA) by branches disproportionately rich in pyrimidine nucleotides.[33, 34] The structure of the nucleic acids is thus extraordinarily manifold and complex, and their conjugation with proteins to form nucleoproteins multiplies these complexities. The resulting myriad variations in composition determine the biologic activity and species specificity of the individual nucleic acids and nucleoproteins, and characterize the chromosomal bearers of heredity.

The known metabolic pathways of the biosynthesis of nucleic acids have recently been reviewed by Brown et al.[35] The simple carbon and nitrogen precursors already mentioned in connection with direct synthesis of uric acid (glycine, formate, ammonia) are also readily incorporated into the same positions of the molecule of the constituent purines of the tissue nucleic acids, adenine and guanine. This strongly suggests common pathways of biosynthesis of nucleotides and nucleic acids, and a presumptive common intermediate.

Of the purine precursors of nucleic acids, only adenine is incorporated significantly, contributing to the polynucleotide (particularly PNA) guanine as well as to adenine. All other purine and pyrimidine components are incorporated appreciably, however, in the form of their nucleotides, again suggesting common pathways, at least in PNA synthesis, involving nucleotide intermediates. The factors that determine the disposition of such intermediates may well prove to have special significance in relation to gout.

The degradation of pentose and desoxypentose nucleic acids bears upon the problem of gout only in respect to their purine components, since the pyrimidines are metabolized by pathways leading to urea, not uric acid formation. The steps involved in the formation of uric acid, the end product of nucleic acid degradation in man, are presumed to be essentially those to be described subsequently in connection with the degradation of "exogenous" preformed nucleoproteins and nucleic acids. The turnover rate of the endogenous nucleic acids is a critical factor in determining the rate of urate formation from this source. This is relatively slow, particularly in respect to DNA, in the healthy adult but evidently is greatly accelerated in certain diseases, notably of the hematopoietic system. Attention has already been directed to the importance of this acceleration in the development of secondary gout.

Degradation of Dietary Preformed Nucleoproteins: This involves a complex series of enzymatic depolymerizations, dephosphorylations, deaminations and phosphorylations which take place in the lumen or wall of the gut (figure 4). In the stomach, pepsin acts upon the nucleoproteins to form nucleins, large molecular protein-nucleic acid complexes. In the small intestine, the protein moiety is split off by trypsin, separating nucleic acids which are then degraded by nucleodepolymerases, ribonucleases and desoxyribonucleases, to oligonucleotides and finally to the mononucleotides adenylic acid, guanylic acid, and the corresponding phosphodesoxyribosides of adenine

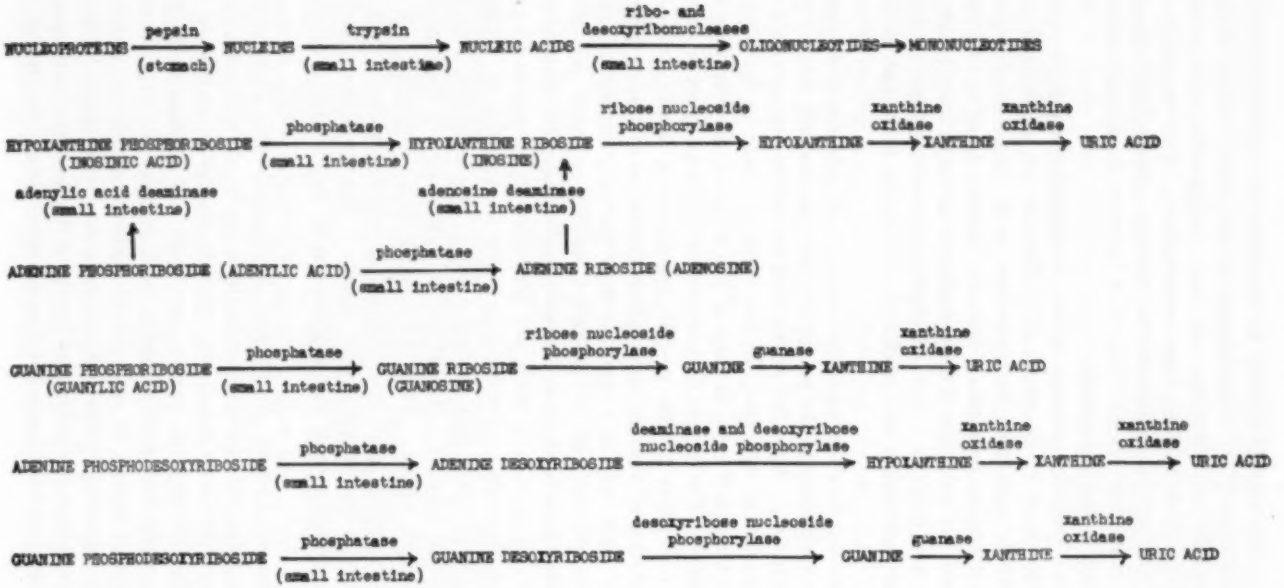

FIG. 4. Schematic representation of the degradation of ingested preformed nucleoproteins. Top line represents the steps leading to formation of the mononucleotides. Remaining lines indicate main pathways of conversion of the principal purine phosphoribosides and phosphodesoxyribosides to uric acid. (From Gutman and Yü.[1])

and guanine. Some of these nucleotides appear to be absorbed as such directly; others incorporating aminopurines appear first to be deaminated; most are probably dephosphorylated in the small intestine to the corresponding purine ribosides and desoxyribosides. The nucleosides so formed, inosine and guanosine (and their desoxyriboside equivalents) are then converted to hypoxanthine and guanine, respectively. This step formerly was believed to be catalyzed by purine "nucleosidases," but Kalckar has shown that conversion to the free purine involves phosphorolysis by ribose and desoxyribose nucleoside phosphorylases, with formation of ribose-1-phosphate or desoxyribose-1-phosphate. Hypoxanthine is oxidized to xanthine and then to uric acid by xanthine oxidase; guanine is deaminated by guanase to xanthine, which is then converted to uric acid. In most mammals uricase is present in the liver and kidney to convert uric acid to allantoin, but in man and the higher apes uricase appears to be absent (except in the bacterial flora of the intestinal tract), and most of the uric acid formed is excreted as such. The Dalmatian hound also excretes significant quantities of uric acid in the urine, not for lack of tissue uricase, however, but because of a species-inherent defect in renal tubular transport mechanisms for reabsorption of urate.[86]

As already indicated, man is not dependent upon the ingestion of preformed nucleoproteins for his supply of purines and nucleic acids but, as has long been known, can be maintained indefinitely without weight loss, impairment of growth, or other detriment on diets low in purine content. On such a low purine diet the renal excretion of "endogenous" urate, a quantity representing something less than the total over-all production of urate by various metabolic routes, remains substantial: 0.3 to 0.5 gm. urate/24 hours in normal human adults. This range is exceeded in some 25 per cent of gouty subjects.[1] It would therefore appear that the bulk of urate production, normally and in gout, derives from endogenous sources ultimately biosynthesized from a variety of simpler nonpurine precursors. The dietary intake of preformed nucleic acids and purines has, nevertheless, an important secondary influence on the course of gout, since ingestion of a heavy meal of purine-rich foods greatly increases urate production, as much as 100 per cent in some instances. This places a heavy extra burden on the excretory routes which, if they are inadequate to the load, leads to a further rise in serum urate levels [87] and accelerated deposition of urate in the tissues. Thus the degradation of "exogenous" preformed purines, the magnitude of which is determined by the diet, is a significant accessory factor in the development of both primary and secondary gout.

Rôle of the Kidney in Gout

As the principal excretory organ for urate, the kidney plays an important rôle in purine metabolism. It is generally assumed that there is complete filtration of urate at the glomerulus, and modern methods of measurement of discrete renal functions, recently summarized by Homer Smith,[88]

indicate subsequent tubular reabsorption of all but 5 to 10 per cent of the filtered urate load. The tubular transport mechanisms concerned have been shown to be of high but limited capacity,[39] with a Tm urate of approximately 15 mg./min.; they are presumed to be enzymatic but have not been identified. It is doubtful that the tubular reabsorptive capacity for urate ever is saturated in normal man, or even at the high plasma urate levels occurring in gouty subjects [40]; however, this may occur in rare cases of severe tubular deficiency with marked impairment of tubular reabsorptive capacity for urate,[40] the human equivalent in this respect of the Dalmatian hound. Tubular secretion of urate occurs in birds and reptiles but has not been unequivocally demonstrated in man,[40] although this has been claimed.[41]

A curious paradox is presented by the husbanding of filtered urate, over 90 per cent of which is reabsorbed by the renal tubules in normal man and in most gouty subjects. In mammals other than man and the higher apes, urate reabsorption presumably is necessary for conversion to allantoin, but in man uric acid is an end product of purine metabolism, without known utility, yet it is conserved with an efficiency comparable to that exhibited for essential electrolytes and metabolites. Certainly in chronic gout preservation of this high reabsorption ratio for urate would seem to be distinctly deleterious, and modern uricosuric therapy is designed to counter persistence of this specific tubular activity.

Application of the most refined methods available has thus far failed to disclose any intrinsic renal defect characteristic of primary gout. In the later stages of the disease renal damage is common, of course, and this is accompanied by significant decreases in glomerular filtration rate, renal plasma flow and tubular excretory capacity.[42] The uric acid clearance, however, which in most normal subjects is in the range 7 to 10 c.c./min. at adequate urine flows, usually is substantially preserved even in advanced cases of chronic tophaceous gout.[1]

If there is little indication of an intrinsic specific renal defect in urate excretion in primary gout, there is even less evidence for this in the case of secondary gout. Nevertheless, in both primary and secondary gout the capacity of the kidney to excrete the loads of urate delivered to it is an important factor in the course of the disease. So long as the excretory pathways can clear the plasma urate at an adequate rate, urate retention and deposition in the tissues is minimized. Should urate production, by any one of the several metabolic routes described, become excessive, adequate clearance of urate becomes increasingly difficult, and deposition of urate in the tissues is accelerated; this becomes apparent, in time, in the development of the deformities and disabilities of chronic tophaceous gout. Deterioration of the kidney with age, due to sclerosis of the renal vasculature, and chronicity of the disease, due to urate deposits in the kidneys and local tissue inflammatory responses, favor urate retention. In secondary gout, as has already been mentioned, vigorous treatment of the underlying disease may

precipitate acute gouty arthritis and lead to the rapid development of tophaceous deposits. Blockage of the ureters with uric acid crystals, which may occur under these circumstances,[43] is not in itself a manifestation of gout but occasionally is accompanied by typical gouty symptoms.

Management of Primary and Secondary Gout

Primary Gout: The current principles of management in primary gout were recently reviewed,[37] and the use of the three effective agents now available for control of the acute gouty attack—colchicine, ACTH and phenylbutazone— was there described in some detail. By appropriate use of one or more of these agents it is now possible to terminate almost all acute seizures more rapidly and with fewer residual discomforts than hitherto.

Colchicine traditionally is given orally in doses of 0.5 mg. or 1.0 mg. every two to four hours until the attack subsides or diarrhea, nausea or vomiting ensues—ordinarily for a total dosage of 6 to 8 mg. A significant proportion of gouty subjects, however, cannot tolerate therapeutic dosages of colchicine, or they respond only partially to full doses. Thus, of 87 attacks in 46 gouty subjects treated with colchicine in our Clinic, in at least one fourth there was some persistence of swelling and pain in the affected joint, sometimes for weeks. Moreover, the debilitating toxic effects of the drug may continue unduly. In this respect the use of intravenous colchicine preparations may be less troublesome, as are the alternative drugs now available.

ACTH is effective in most acute gouty attacks, even those refractory to colchicine, if given in adequate amounts according to a proper dosage schedule. Depending upon severity, duration of symptoms and response, 50 to 200 mg. (usually 100 mg.) are injected on the first day of treatment, and daily doses of 50 to 100 mg. are then given for the next day or two. Thereafter it is usually possible to taper off the dosage, concurrently giving small doses of colchicine (1 to 2 mg. daily). In many instances, particularly in minor seizures, a single injection of 100 mg. ACTH in long-acting gel form will suffice to terminate the attack.[44] If the suppressive action of ACTH is discontinued too abruptly, there is apt to be a recrudescence of symptoms, as observed in many other diseases insufficiently treated with ACTH. In our experience of 40 acute attacks occurring in 33 gouty subjects treated with ACTH, 10 to 15 per cent failed to respond satisfactorily despite full and maintained therapy.[37]

Phenylbutazone, in daily oral doses of 0.6 to 0.8 gm., usually gives rapid relief of the acute attack.[45] Thus, in our own experience,[37] of 20 acute episodes occurring in 16 gouty subjects, in 13 there was complete or virtually complete remission within 24 to 48 hours; the seven remaining attacks responded less rapidly and completely. It need hardly be emphasized that, because of its toxicity, phenylbutazone must be used with caution.

However, for the few days of treatment ordinarily required in acute gout the risk appears to be small.

In respect to prevention of acute gouty arthritis in those subject to frequent recurrence, the uninterrupted prophylactic administration of colchicine in low dosage (0.5 to 2.0 mg. nightly) has proved to be useful. A recent report [37] of 31 gouty patients given regular colchicine prophylaxis, together with appropriate restriction of the diet, for periods from 18 months to four years, indicates that in 18 there was marked reduction in the frequency and severity of attacks; indeed, in 13 cases this improvement restored to full employment gouty subjects who had hitherto been virtually incapacitated by frequent interruption of activities due to recurrent acute attacks. In eight patients the results of colchicine prophylaxis were unsatisfactory, and in five instances no definite judgment could be made.

In respect to prevention and treatment of the deformities and disabilities of chronic tophaceous gout, these are now recognized as the result of protracted positive urate balance, and modern therapy is directed toward achieving negative urate balance which is then maintained for as long as may be required. This can be accomplished in most instances by dietary regulation and the regular administration of a uricosuric agent of low toxicity, such as Benemid. Appropriate management of this kind usually obviates the formation of extensive tophaceous deposits, prevents the further enlargement of tophi already formed, and even brings about mobilization of long established tophaceous deposits in some instances.[37, 46, 47]

The importance of avoidance of excessive dietary intake of preformed purines has already been pointed out. It is our practice also to limit the protein intake to 50 to 75 gm. per day, given, so far as possible, in the form of plant and milk product proteins; this restriction is intended to lower the intake of nitrogenous precursors of uric acid (glycine, nucleotides and derivatives) present in abundance in meats, fish and fowl. Fat consumption also is restricted, in part because ingestion of fat tends to cause retention of urate by the kidneys, in part as an anti-obesity measure. The usefulness of such dietary regulation is of necessity limited, because of the lively biosynthesis of uric acid from the simplest precursors derived from virtually every foodstuff. Nevertheless, on such restricted diets the urinary urate excretion ordinarily decreases 200 to 300 mg./24 hours, and serum urate levels show a general downward trend: in a series of 71 gouty subjects so studied,[37] the mean fall in serum urate was 1.2 mg. per cent, with declines in excess of 3 mg. per cent in occasional instances. Recent isotope studies utilizing N^{15}-labeled glycine indicate that high protein diets tend to accelerate the metabolic pathways of purine biosynthesis so that disproportionately large amounts of uric acid are formed from nitrogenous precursors.[48, 49]

The most effective available means for producing negative urate balance, however, is the regular administration, in doses of 0.5 to 3.0 gm. daily, of the potent uricosuric agent, Benemid.[50-53] This drug causes marked and

highly selective suppression of tubular reabsorption of urate, a single orally administered 2 gm. dose rapidly increasing urate clearance to a mean peak approximately four times the premedication level.[40] The mean daily increase in urinary urate excretion in the first week of administration is 46 to 67 per cent, depending upon dosage.[50, 51] This is usually associated with a rapid and sharp decline in serum urate, with appropriate dosage to levels approximating the normal, and such serum levels can ordinarily be maintained, apparently indefinitely, by continued administration of the drug. The incidence of side reactions, chiefly gastrointestinal discomfort and occasional drug sensitivity, is so low as to make protracted daily use—a prerequisite to successful uricosuric therapy—entirely feasible in most patients. Benemid is still too newly introduced for definitive evaluation of its place in the management of chronic gouty arthritis, but the experience thus far indicates a more hopeful outlook for the gouty patient in respect to the discomforts due to tophaceous deposits.[37, 53]

Secondary Gout: It has been the general experience, including our own, that acute gouty arthritis occurring in the course of polycythemia, leukemia, myeloid metaplasia, pernicious anemia, chronic hemolytic anemia, etc., responds to colchicine in much the same way as in primary gout. We have had occasion also to use ACTH in acute gouty attacks associated with chronic myeloid leukemia, with relief of symptoms. It would therefore appear, so far as can be ascertained from the limited experience on record, that there is no essential difference in the response of acute seizures in primary and secondary gout to the therapeutic agents usually employed for this purpose.

Of course, the presenting problem in secondary gout is the treatment of the underlying disorder. Attention has already been called to the fact that vigorous therapy of the primary disease may precipitate acute gouty arthritis, accelerate the deposit of uric acid in the urinary tract and joints, and otherwise accentuate the course of gouty complications. The use of uricosuric agents in secondary gout carries an enhanced risk of ureteral block by uric acid crystals and therefore is not advised unless special precautions are taken.

Summary

1. The clinical syndrome of gout appears to comprise several distinct anomalies of purine metabolism. The usual form of the disease reflects an inborn error of purine metabolism and may be regarded as primary gout. Secondary gout may develop occasionally in the course of diseases involving the hematopoietic system, and in related disorders.

2. The major pathways of purine metabolism are reviewed. The metabolic pathways for direct biosynthesis of purines appear to be chiefly involved in primary gout; those concerned with the biosynthesis and degradation of "endogenous" nucleic acids seem to be largely responsible for secondary

gout; the processes involved in degradation of ingested preformed nucleoproteins may affect the course of both primary and secondary gout.

3. The rôle of the kidney in gout is described. There is no convincing evidence for an intrinsic renal defect characteristic of either primary or secondary gout. Nevertheless, retention of urate by the impaired kidney may have a deleterious effect on the course of both forms of gout.

4. The principles of management of the acute and chronic manifestations of gout are reviewed. So far as can now be ascertained, the therapeutic response to the usual measures is essentially the same in both primary and secondary gout. Special problems arise, however, in the management of secondary gout in connection with treatment of the underlying disorder.

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HEPATOMEGALY AND DIABETES MELLITUS *

By Joseph I. Goodman, M.D., F.A.C.P., *Cleveland Heights, Ohio*

It was fully recognized in the older literature that the liver is frequently increased in size, and sometimes tender, in patients with diabetes mellitus.[1-3] In fact, in 1885 Pavy [4] found liver enlargement associated with diabetes often enough to warrant his postulating a connection between the two conditions. However, in the recent clinical literature there have been relatively few references to hepatic enlargement in diabetes mellitus.[5-7, 14, 18, 22, 26] Of more pertinent value in this respect are the reports of animal experiments. Following total extirpation of the pancreas in dogs the liver remains large out of all proportion to the general body weight.[8-9]

In view of the constancy with which a large, fatty liver occurs in diabetic animals, one should expect to find a similar situation in the diabetic human.

Method

The purpose of this study is to determine clinically a possible relationship between hepatomegaly and the state of diabetic control. A series of 459 diabetic patients was examined for the presence or absence of heptomegaly. There were 319 males and 140 females in the study, the preponderance of males being due to the inclusion of 129 patients from a Veterans Administration (Crile) hospital. Even with the deletion of the latter there is still a preponderance of males (190) over females (140) in this series. The patients are separated into three groups, based upon the state of their diabetic control: (1) *controlled* diabetes (379 patients); (2) *uncontrolled* diabetes (70 patients); and (3) *keto-acidosis* (10 patients).

The patients are separated arbitrarily into "controlled" and "uncontrolled" diabetics on the basis of the total glycosuria in a 24 hour period. Patients in whom the glycosuria exceeds 50 gm. of glucose in 24 hours are classed as uncontrolled, those with 50 gm. or less as controlled. The separation of the patients with keto-acidosis presents no problem. Note was taken of patients who had a history of the common clinical symptoms of diabetes, namely, weight loss, polyphagia, polydipsia, polyuria, generalized weakness, fatigue, "loss of pep," lethargy and pruritus vulvae. Also, the presence of diabetic neuropathy was recorded. Undoubtedly, the above-mentioned symptoms are strongly indicative of uncontrolled diabetes, and we believe that neuropathy as well occurs only in patients whose diabetes is poorly controlled.[10] In a previous study malnutrition and obesity were found to be responsible for hepatomegaly in some diabetic patients.[7] The possible rôle of these two factors must be taken into consideration in any evaluation of the final results.

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The size of the liver was measured carefully by percussion of the liver dullness in the midclavicular line. According to our standards (reported previously), the upper limit of liver dullness in the normal male is 7.5 cm. and in the female 7.0 cm.[7] It must be emphasized that these measurements do not represent actual size of the liver; they are merely an index of the liver dullness, increasing and decreasing with corresponding changes of its volume.

Results

Well Controlled Diabetes (379 Patients): In 379 well controlled diabetic patients (less than 50 gm. of glucose in the 24 hour urine) the liver size was normal in 346 patients (91 per cent) and enlarged in 33 patients (9 per cent). (See table 1.) Of the 33 patients in whom hepatomegaly was detected, obesity may conceivably have caused the hepatomegaly in 12, malnutrition in eight, hemochromatosis in one and diabetic nephropathy with edema in one. There was no apparent explanation for the presence of an

Table I

Patients with Controlled Diabetes

Number of Diabetes Controlled Patients		379
Normal	346 patients (91 per cent)	
Enlarged	33 patients (9 per cent)	
Obesity	12 patients	
Malnutrition	8 patients	
Nephropathy with Edema	1	
Hemochromatosis	1	
Unexplained	11 (3 per cent)	
Patients with Clinical Symptoms of Diabetes		2
Patients with Diabetic Neuropathy		3

enlarged liver in the remaining 11 patients (3 per cent of the controlled cases), although the possibility remains that they may represent the margin of error inherent in the method employed to ascertain liver enlargement. Nevertheless, as additional evidence that these 379 patients were in reality well controlled at the time their liver size was estimated, we cite the extreme rarity of patients with clinical symptoms of diabetes (two cases) and neuropathy (three cases).

Uncontrolled Diabetes (70 Patients): The 24 hour excretion of glucose in the urine exceeded 50 gm. in 70 patients. Hepatomegaly was detected in 45 patients (60 per cent) of this group, and a normal liver size was recorded in 27 (40 per cent) of the cases. (See table 2.) Since other factors, such as malnutrition (four cases) and obesity (three cases), may conceivably have produced the hepatomegaly in only seven patients, the incidence of liver enlargement exceeds 50 per cent of the uncontrolled patients even if these cases are omitted. From these data the conclusion is obvious that hepatomegaly occurs in a high percentage of cases of uncontrolled

TABLE II

Patients with Uncontrolled Diabetes (50 or more Gm. of Glucose in 24 Hour Urine)	
Number of Patients	70
Liver Size (by Percussion)	
Normal	27 patients (40 per cent)
Enlarged	43 patients (60 per cent)
Patients with Clinical Symptoms of Diabetes	33
Patients with Diabetic Neuropathy	16

diabetes. Further confirmation of the fact that in Group 2 the diabetes was actually out of control is provided by the presence of clinical diabetic symptoms in 33 patients and of neuropathy in 16 of the 70 patients.

In the course of the study the question arose whether 50 gm. of glucose, the amount arbitrarily selected, is a valid criterion of poor diabetic control. In this connection it is noteworthy that 11 patients who excreted more than 50 gm. of glucose in 24 hours not only had a normal liver measurement but also failed to give a history of either diabetic symptoms or neuropathy. From this it would appear offhand that the cardinal symptoms of diabetes and the presence of neuropathy, as well as hepatomegaly, are all better criteria of poor diabetic control than the amount of glycosuria. Tolstoi has long argued that the clinical symptoms are a better indication of good or poor diabetic regulation than the amount of glycosuria, and claims that many patients, though excreting relatively large amounts of glucose, get along very well.

Conversely, in our series there were six patients spilling less than 50 gm. of glucose in the 24 hour urine who presented either diabetic symptoms or neuropathy, with or without liver enlargement. In the patients excreting less than 50 gm. of glucose in the 24 hour urine collection, hepatomegaly and clinical symptoms of diabetes were both present in three patients, hepatomegaly and neuropathy in one, and hepatomegaly associated with both the

TABLE III

Patients Showing 50 or More Gm. of Glucose in 24 Hours Urine (Uncontrolled) Without Symptoms of Diabetes, Neuropathy or Hepatomegaly	12 cases
Patients Showing 50 or More Gm. of Glucose in 24 Hours Urine (with Hepatomegaly):	
With Neuropathy	2
With Diabetic Symptoms	3
With Diabetic Symptoms and Neuropathy	2
	7
Patients Showing Less than 50 Gm. of Glucose in 24 Hours Urine with Hepatomegaly:	
With Diabetic Symptoms	3
With Neuropathy	1
With Neuropathy and Clinical Symptoms	1

clinical symptoms of diabetes and neuropathy in two cases. (See table 3.) One of the latter is a physician who had mild diabetes of 20 years' duration which had been controlled on diet alone prior to the development of a severe neuropathy, at first unrecognized. Every possible cause for the severe pain except the diabetes had been ruled out before he consulted us. This patient had only 36 gm. of glucose in the 24 hour urine specimen in the face of a typical femoral neuropathy, a story of recent weight loss and an enlarged liver. After the administration of a small daily dose of regular insulin the hepatomegaly regressed within one week and the neuropathy cleared up gradually. Of interest is the fact that during the first week of rapid clinical improvement the glycosuria diminished only slightly (from 36 to 28 gm.). This case seems to substantiate the aforementioned opinion, that the cardinal diabetic symptoms, the presence of neuropathy or hepatomegaly, may prove to be better criteria of poor diabetic control than the amount of glycosuria.

It cannot be ascertained from our data which of these three clinical manifestations is the better indication of poor diabetic control. Patients were encountered who had hepatomegaly without symptoms of diabetes or neuropathy. Among the uncontrolled patients (excreting more than 50 gm. of

TABLE IV

Keto-Acidosis		
Number of Patients		10
Liver Size (by Percussion)		
Normal		None
Enlarged	10 Patients	(100 per cent)

glucose in the 24 hour urine) there were two who had neuropathy alone, three with clinical symptoms of diabetes, and two who presented both the cardinal symptoms of diabetes and neuropathy without liver enlargement.

Keto-Acidosis (10 Patients): Each of the 10 patients in this group showed marked hepatomegaly. In fact, the largest livers which we encountered occurred in this group.

DISCUSSION

Pathologic Changes in the Hepatomegaly of Diabetes Mellitus: In a previous study,[7] four causes of hepatomegaly were identified in diabetic patients: (1) malnutrition, (2) obesity, (3) cirrhosis, and (4) poorly regulated diabetes or acidosis. Malnutrition was associated with hepatomegaly in 11 of 101 diabetic patients. This condition is, of course, analogous to the fatty livers of diabetic animals maintained on a choline-deficient diet. Similar changes in the liver occurred during World War II in prisoners who had lived on a protein intake of less than 30 gm. daily for two to four years.

As for obesity, from the studies of Newburgh and his associates,[11] who

described a decreased glucose tolerance in such patients and attributed this to fatty infiltration, a higher incidence of liver involvement can be anticipated in obese individuals. Among the 101 diabetic patients mentioned previously,[7] hepatomegaly was found in 13 obese patients. It was concluded therefrom that, whereas obesity can produce moderate enlargement of the liver, significant degrees of hepatomegaly are present only in some of the extremely obese persons.

The results of the present studies agree with the observations of other authors showing that fatty deposits occur in the livers of untreated and uncontrolled diabetic patients.[12-15] It is well known that in the dog, shortly after pancreatectomy, the glycogen content of the liver is greatly diminished and there is a rapid infiltration of fat which is not prevented by the feeding of raw pancreas, choline or methionine.[16] As a result of insulin deprivation, fatty acids are poured into the liver at a rapid rate. Gibbs and Chaikoff [16] report that the liver of one dog contained 20 per cent fatty acids only two days after the last insulin injection, and after five days the liver of another dog contained 39 per cent.

Prolonged fatty infiltration of the liver has been shown to be a precursor of cirrhosis in diabetes mellitus.[17-20] Connor [17] emphasizes the fact that cirrhosis occurs with more than usual frequency in diabetic patients (from 0.5 per cent to 12.7 per cent [15]). Schleusner [21] found 45 cases of Laennec's cirrhosis in 355 autopsies (12.7 per cent), and the onset of the diabetes preceded the cirrhosis in 20 cases. Macroscopically, the livers are enlarged and fatty, and show the typical hobnail appearance of Laennec's cirrhosis, especially at the edges. Histologically, one finds a characteristic increase in connective tissue around the portal spaces subdividing the liver into small nodules. The fibrosed portal spaces contain a large number of irregular proliferated bile ducts, and there is also an infiltration of lymphocytes.

Incidence of Hepatomegaly in Cases of Uncontrolled Diabetes Mellitus: In the present study the incidence of hepatomegaly in patients with uncontrolled diabetes is 60 per cent (43 out of 70 cases), as compared with 9 per cent (33 out of 346 cases) in the patients with controlled diabetes. Obviously, enlargement of the liver occurs very frequently in untreated or poorly managed diabetic individuals. The studies of Gray, Hook and Batty [20] substantiate these findings of a high percentage of liver abnormalities in uncontrolled diabetic persons. By means of the colloidal gold test these authors found hepatic involvement in 57.1 per cent of a poorly controlled group of diabetic patients and in 26.3 per cent of a well controlled group. The effect of poor diabetic control on the liver has been observed previously by White and others, principally in children. I was unable to find any significant statistical difference in the incidence of hepatomegaly in the young and older age groups in this series. Gray et al. had a similar experience with respect to liver function. I believe the emphasis of others on hepatomegaly in juvenile diabetic patients stems from the use of palpation in the detection

of liver enlargement. The liver of a child is readily palpable, whereas in the adult the liver frequently eludes the palpating fingers of the examiner.

It has been noted in the poorly controlled diabetic patients studied herein that the large liver reverts to normal size following a short period (seven to 10 days or less) of treatment. The administration of lipotropic substances does not appear to hasten this transition, and in my opinion there is no indication for such treatment in the absence of malnutrition. Allen's experiments [31] proved conclusively that a small pancreatic remnant enables a dog to keep a normal liver as long as 12 years *without any dietary supplement.*

Hepatomegaly in Diabetic Keto-Acidosis: The association of abdominal symptoms with diabetic keto-acidosis has been recognized for some time by many clinicians.[18, 32-36] Bothe and Beardwood [37] reported a series of 136 cases of diabetic keto-acidosis in which 96 (74 per cent) presented nausea, vomiting and abdominal pain and tenderness, usually associated with leukocytosis and fever. Once the keto-acidosis had been overcome the abdominal symptoms disappeared rapidly. Because the symptoms of keto-acidosis may simulate the clinical picture of an acute abdominal condition the diagnosis should be suspected in every diabetic patient having nausea, vomiting and abdominal pain. The practical implications of this differentiation are brought out emphatically in Bothe and Beardwood's report of 18 diabetic patients in keto-acidosis who were operated on erroneously for intestinal obstruction, acute cholecystitis, acute appendicitis, peritonitis or acute pancreatitis.

From the foregoing it is clear that the differentiation of diabetic keto-acidosis with abdominal symptoms from an acute surgical abdominal condition presents a serious problem. All the patients studied by Bothe and Beardwood were examined carefully for lesions of the gastrointestinal and genitourinary tracts following recovery from keto-acidosis but a satisfactory explanation for the abdominal symptoms was not found. The percentage of gall-bladder disease, for example, was not much greater than that found in any control series of adult diabetic patients.

In the absence of a satisfactory explanation of the abdominal symptoms in diabetic keto-acidosis several theories have been advanced: (a) acute pancreatitis; (b) intense spasm of the gastrointestinal tract; (c) a defense mechanism to rid the body of acid ions by way of the gastric juice. Beardwood's studies eliminate the possibility that organic gastrointestinal disease underlies these symptoms, and the other hypotheses have had few supporters.

The presence of a greatly enlarged, frequently tender liver in every case of keto-acidosis encountered in my material [7] strongly suggests that this organ may play a rôle in the abdominal symptoms which occur in this condition. Prior to 1922 the large, fatty liver was a typical finding at autopsy in patients who died from diabetic coma. Reinberg and Lipson [29] reported recently that 52 (51.0 per cent) of 102 diabetic patients who were in coma

or acidosis prior to death had fatty livers at autopsy. Beardwood mentions, incidentally, that two of the children in his series with acidosis had enlarged livers. Further support for the concept that the abdominal symptoms are produced by liver abnormalities is supplied by the exceedingly high incidence of hepatic disease found by Gray, Hook and Batty [30] in 22 patients with acidosis or coma. The colloidal gold test was positive in 17 instances (77.2 per cent) of this group. The rapid diminution of liver size which we observed in the cases of keto-acidosis is not inconsistent with the rapid subsidence of the abdominal symptoms after treatment.

The occurrence of liver abnormalities in uncontrolled diabetes suggests a possible explanation for the relatively mild, persistent digestive disturbances referred to by Bassler and Peters [38] as "diabetic indigestion." In this subtle condition, organic diseases having been ruled out, the digestive disorders were relieved rapidly only by antidiabetic measures, which strongly suggests a relationship between these "obscure" abdominal complaints and the liver abnormalities associated with poor diabetic control.

The Value of Palpation Versus Percussion in the Determination of Liver Size: The normal weight of the liver is given as 1,200 to 1,600 gm.[22] When a liver becomes infiltrated with fat the additional fat is deposited intracellularly. Consequently, in each unit of liver volume there is an increase of cell volume at the expense of extracellular space and a resulting increase in the over-all size of the organ. Since hepatomegaly in diabetes mellitus is usually due primarily to gross fatty infiltration,[15-23] it naturally follows that such a liver would be increased in volume (size). Unfortunately, for the determination of liver size one is forced to utilize its clinical palpability, percussion of hepatic dullness or its roentgenographic appearance. The latter procedure has proved to be of little practical importance.

The most generally employed criterion of liver enlargement is the palpability of its lower border. As long ago as 1896 it was pointed out that the liver might be palpable without being greater than average in weight.[24] Subsequent observations show only a rough correspondence between liver enlargement and palpability.[25-27] In a study of Laennec's cirrhosis Ratnoff and Patek [25] compared the clinical palpability of livers and spleens with the size of the organs as observed at autopsy. Errors occurred in both directions, that is, palpable organs were frequently not enlarged and enlarged organs were frequently overlooked by palpation. For example, they found 78 palpable livers to vary in weight from 895 to 5,100 gm., while 30 nonpalpable livers weighed 570 to 2,920 gm. In agreement with these reports, Zelman's studies [28] also revealed a poor correlation of clinical palpability with actual enlargement of the liver. Reinberg and Lipson [29] presented postmortem evidence showing the unreliability of palpation in both the fatty and the cirrhotic liver. Although a fair correlation between palpation of the liver edge clinically and at autopsy was found, their data prove clearly that a palpable liver bears no constant relationship to its weight and size. There-

fore, the palpability of the liver is an unreliable method for the determination of hepatomegaly and occasionally may even lead to an incorrect diagnosis.[25]

Many errors inherent in the use of palpation of the liver appear to be avoidable by use of the percussion technic previously described.[7] Since percussion of the liver dullness is based upon the bulk of the organ, it is immaterial whether the liver is situated above or below the costal margin. Still, it should be emphasized that the position of the liver is not static. Apparently the organ is quite mobile and its ultimate position dependent upon various intrathoracic and intra-abdominal forces such as emphysema, obesity, pregnancy, development and tension of the abdominal musculature, the nutritional state, etc. Actually, by means of percussion I have been able to detect enlarged livers located well above the costal margin or to recognize a normal liver located far below the costal margin. Although the high incidence of palpable but normal size livers is impressive, the great frequency of livers situated above the costal margins, as in the majority of obese individuals, is even more striking. From a practical standpoint the mobility and position of the liver greatly affect its palpability but do not appear to impair the value of percussion in the measurement of liver dullness.

The opportunity does not arise frequently to verify the accuracy of our method for the determination of the liver size. Such an occasion presented itself in a well controlled male diabetic patient in whom a normal liver had been percussed one day before his sudden death as a result of a myocardial infarction. At autopsy the liver weighed 1,270 gm. and was otherwise normal in every respect. In several other cases in which a normal liver was believed to be present clinically normal liver function tests were reported, although such tests were not performed routinely in the present series. In a fatal case of hypoglycemia the antemortem finding of a normal liver was substantiated at autopsy.

Liver Function Studies in Diabetes Mellitus: Although hepatic enlargement in diabetes mellitus has been emphasized by several authors, corroborative evidence of this finding by liver function studies is relatively sparse. Hanssen [39] found a normal icteric index and urobilinogen excretion in his diabetic patients with hepatomegaly. Marble [14] reported normal plasma bilirubin determinations in eight patients and normal cholesterol/ester ratios in 29 out of 30 patients. Rabinowitch [41] reported positive van den Bergh reactions in 34 out of 130 diabetic patients but noted abnormal urobilinogen excretion in only three out of 50 patients. Diamond [42] found normal van den Bergh reactions in 14 out of 17 diabetic patients. However, in three severe, untreated cases the bilirubin was slightly elevated and, even more interesting from our point of view, the urobilinogen was invariably elevated during ketosis and disappeared promptly upon the administration of insulin. Meyer [43] observed abnormal hepatic dysfunction based upon quantitative van den Bergh reactions and urobilinogen excretion studies in 28 out of 100 patients with diabetes.

Some of the observations just mentioned are suggestive of liver damage in diabetes mellitus, but the studies of Gray and his co-workers [20] are more nearly analogous to my data on hepatomegaly. By means of the colloidal gold reaction evidence of hepatic dysfunction was demonstrated in 148 (38.9 per cent) out of 380 diabetic patients. As in hepatomegaly, the colloidal gold test was positive in a higher percentage of obese patients (48.4 per cent) compared with the non-obese (34.8 per cent). Just as hepatomegaly was six times more prevalent in the uncontrolled diabetics in this series, hepatic disease proved to be more prevalent in Gray's severe diabetic group. Thus the colloidal gold reaction was positive in 62 out of 123 patients with severe diabetes (49.9 per cent), compared with 29 out of 124 patients with mild diabetes (23.3 per cent). In some of their cases in which efforts to control the diabetes were futile these authors report an exaggeration of liver dysfunction.

Obviously, it is essential that the best possible liver function be maintained in every diabetic patient. From the present studies it can be concluded that patients in whom the diabetes is well controlled will in all probability have normal liver function. In fact, Leevy et al.[19] have suggested the use of hepatic function studies from time to time as a guide in evaluating the degree of control of diabetic patients.

Summary

1. A series of 459 unselected diabetic patients was examined for hepatomegaly by percussion of the area of liver dullness.

2. The patients were classified as controlled (379 patients), uncontrolled (70 patients), and keto-acidosis (10 patients).

3. Liver enlargement was noted in 33 (9 per cent) of the patients with controlled diabetes; 45 (60 per cent) of those with uncontrolled diabetes, and 10 (100 per cent) of patients with keto-acidosis.

4. From the data in this study it would appear that the cardinal symptoms of diabetes (polyuria, polydipsia, etc.), the presence of neuropathy or hepatomegaly are better indications of the state of the diabetic control than the total amount of glucose excreted in 24 hours.

5. The results correlate well with the pathologic reports, all of which prove that fatty deposits occur in the liver of untreated or uncontrolled diabetes mellitus.

6. The imperfections and unreliability of palpation of the liver in contrast to percussion of liver dullness are discussed.

7. The occurrence of a greatly enlarged, frequently tender liver in every patient with keto-acidosis points to this organ as being a major factor in the production of the abdominal manifestations of this condition.

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ABNORMAL RHYTHMS ASSOCIATED WITH CARDIAC SURGERY AND THEIR TREATMENT*

By J. Scott Butterworth, M.D., F.A.C.P., *New York, N. Y.*

Interest in abnormal cardiac rhythms occurring during surgical procedures has been stimulated in recent years by demonstration that many of these rhythms can be controlled or converted to a normal mechanism by proper therapy—drug, mechanical or electrical. With the emphasis at the present time on cardiac catheterization, angiocardiography and cardiac surgery, these abnormal rhythms have become more common due to mechanical irritation of the heart; therefore, the diagnosis and treatment of these arrhythmias have been the subject of much investigation, with resulting great improvement in technics.

Diagnosis

The abnormal rhythms associated with cardiac catheterization and surgery are, in general, similar to those which may occur spontaneously in the absence of mechanical stimulation of the heart. These rhythms may be due to intrinsic disease of the heart, or may be caused by various types of reflex stimuli, by anesthetic agents and anoxia. In general, the rhythms which originate in the auricles and in the A-V node are of less potential danger than rhythms which originate in the ventricles, since the latter are more apt to lead to cardiac arrest; therefore, this is the major abnormality in rhythm to be prevented.

Figure 1 illustrates the occurrence of ventricular fibrillation leading to cardiac arrest. This record is some 30 years old and is shown with the kind permission of Dr. R. H. Halsey. Figure 2 is another of Dr. Halsey's cases, showing the gradual development of cardiac arrest without ventricular fibrillation. I have purposely used these old records for illustration to emphasize that our present problems are no different from those which have always been present, but that we now have at our command diagnostic and therapeutic tools for handling cardiac arrest.

Without making any attempt to illustrate or to mention all the types of arrhythmias that occur during cardiac surgery (which would really require a listing of most known types of arrhythmias), we are going to illustrate a few of the more common varieties. Figure 3 shows four episodes of runs of ventricular extrasystoles occurring during operation for relief of mitral stenosis by finger fracture of the mitral valve. The basic rhythm is slow auricular fibrillation controlled by digitalis. One can see these short bursts of ventricular beats occurring whenever the surgeon examined or fractured

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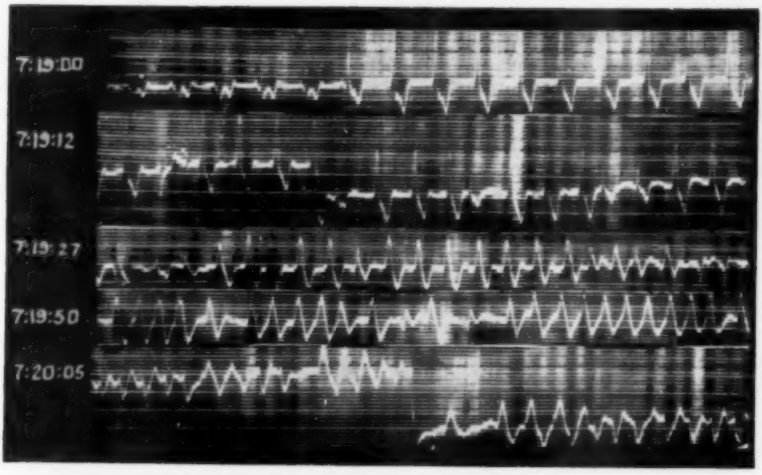

FIG. 1. Terminal electrocardiographic events occurring within a minute ending in ventricular fibrillation and death. (Courtesy Dr. R. H. Halsey.)

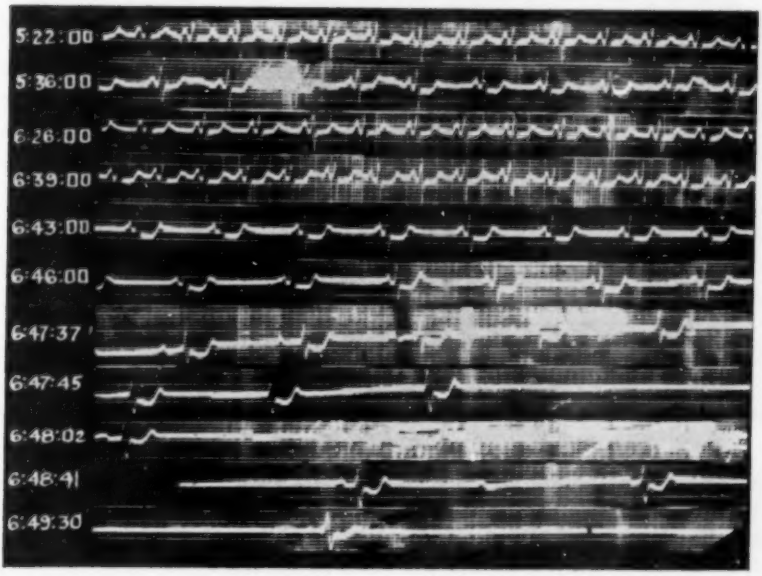

FIG. 2. Terminal electrocardiographic events occurring over a period of one hour 27 minutes and resulting in death from cardiac standstill. (Courtesy Dr. R. H. Halsey.)

the valve and disappearing spontaneously shortly after the finger was withdrawn from the mitral opening. This pattern occurs almost invariably in cases of this type and probably is a result of both mechanical stimulation from the surgeon's finger and the change in hemodynamics produced by the sudden complete occlusion of the mitral opening by the finger of the surgeon.

Figure 4 is a most interesting illustration of various types of rhythms which occurred in another case of attempted mitral commissurotomy, and was kindly lent to me by Dr. C. A. R. Connor and Dr. H. C. Maier. While

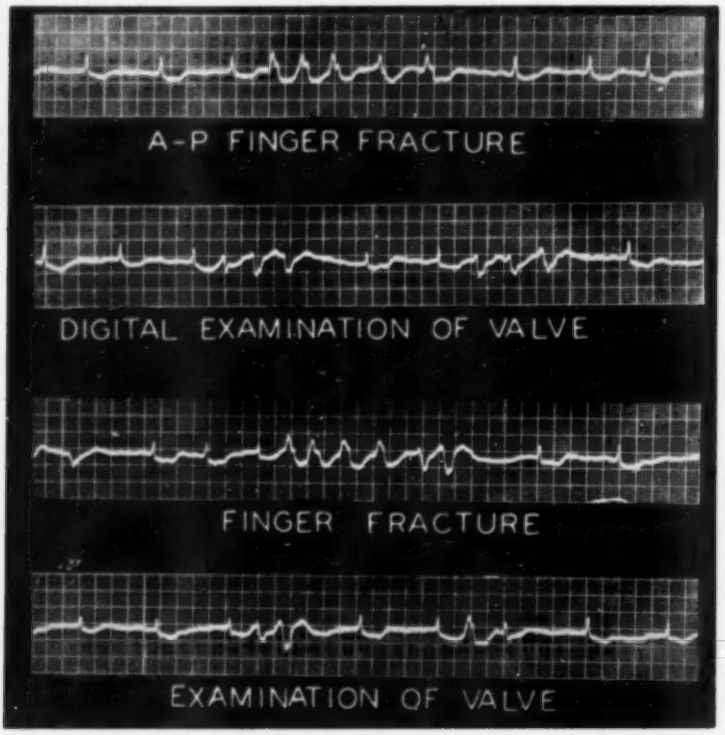

FIG. 3. Four separate episodes during the course of finger fracture of the mitral valve, illustrating the response to occlusion of the mitral ring by the surgeon's finger.

the auricular appendage was being sutured the patient developed ventricular tachycardia and ventricular fibrillation. Cardiac massage was immediately started and epinephrine, followed by calcium chloride, was injected into the chamber of the heart. While this was occurring, intravenous Pronestyl was started. The illustration depicts the train of events. The patient eventually recovered without sequelae.

Probably the most important aspect of treatment of abnormal cardiac

rhythms is accurate, immediate diagnosis. This requires that an instrument for registering the electrocardiogram be immediately available; preferably, the entire operation should be monitored on such an instrument. The newer type of direct writing electrocardiographic instrument is satisfactory, but the long records are a nuisance and we prefer to monitor with a device using an oscilloscope tube, so that a continuous visual tracing is always available for inspection. Recordings can then be made on a direct writer

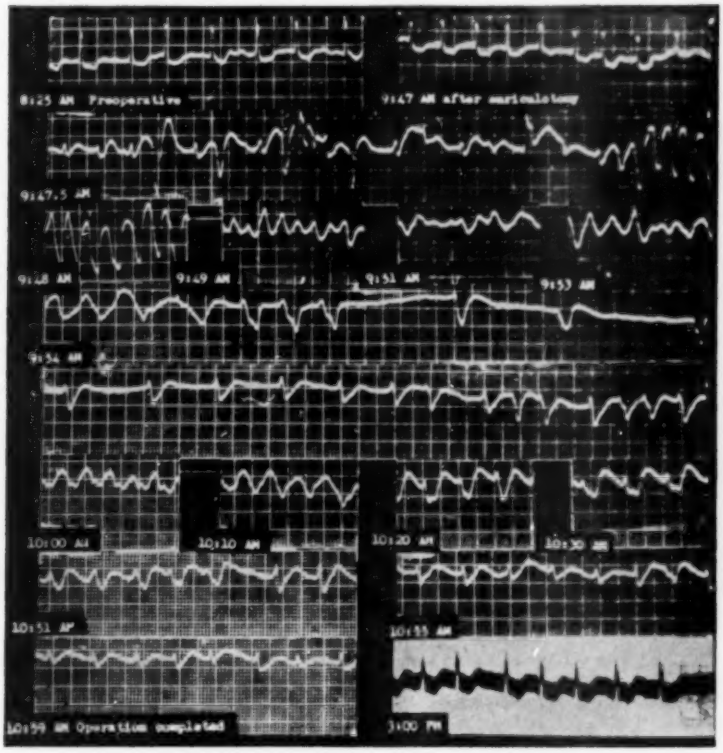

FIG. 4. Sequence of events during attempted finger fracture of the mitral valve. See text for data. (Courtesy Dr. C. A. R. Connor and Dr. H. C. Maier.)

if interesting patterns are shown on the oscilloscope. Recently, Dr. William Proudfit has been recording the electrocardiogram on tape and at the same time visualizing the pattern on the oscilloscope. This gives a permanent record which can be played back immediately if it is desired to review quickly the events of preceding few minutes; or it can be reviewed at one's leisure, and permanent recordings made. If nothing of interest occurred during the operation, the tape can be erased and used again.

At the present time it is our practice to monitor the electrocardiogram on an oscilloscope using a lead from the esophagus which is put in place by the anesthetist just prior to induction of anesthesia (or it may be inserted after induction). Figure 5 illustrates tracings taken from an esophageal lead at various auricular levels. An arrhythmia is present which occurred during a repair of an inguinal hernia, which was transient, did not cause any change in cardiac function and did not require specific treatment. The esophageal lead is helpful because of its ability to pick up the auricular potentials and to record P waves of high voltage.[1, 2, 3]

Figure 6 is an example of how difficult it may be to make an exact diagnosis of an arrhythmia without having esophageal leads. This patient had

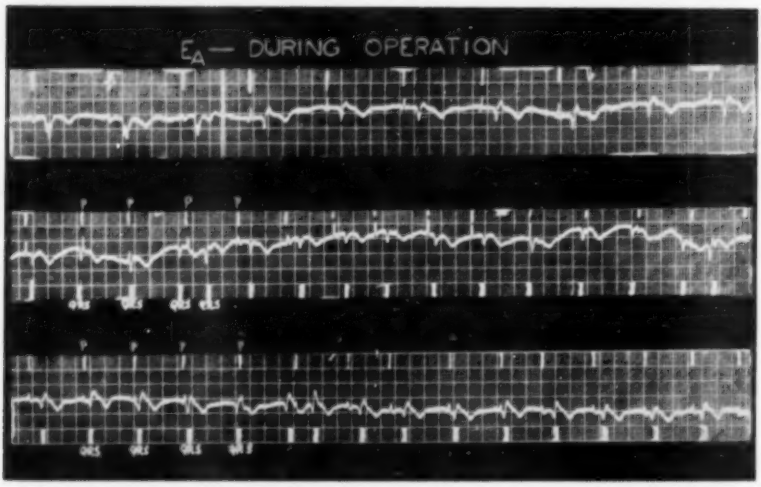

FIG. 5. Esophageal electrocardiogram recorded during an operation for repair of inguinal hernia. The P waves are marked above the tracings and the QRS complexes below the tracings. The voltage of the P wave is usually much higher from a proper esophageal lead than from leads on the surface of the body.

a right bundle branch block which is illustrated at the top right. He developed a tachycardia in which the QRS complexes were also wide (top left). The esophageal lead at the bottom (retouched) shows an auricular rate independent of the fast ventricular rate, and establishes the diagnosis of ventricular tachycardia. Once the exact diagnosis of the abnormal rhythm is made, one is in a position to attempt proper therapy.

THERAPY

It is difficult to be too specific about therapy in these arrhythmias because of the variable response from patient to patient, and even in the same patient at different times. Certain general principles can be outlined, but the person

responsible for determining the type of therapy must be prepared to recognize this variability of response and often to change course on short notice.

In general, we use digitalis preoperatively only in patients with cardiac failure who have previously been on digitalis; or in patients with chronic auricular fibrillation or flutter, where it is used to control the ventricular rate. We do not digitalize a patient preoperatively with the hope that it may prevent difficulties; we prefer to wait until some specific abnormality

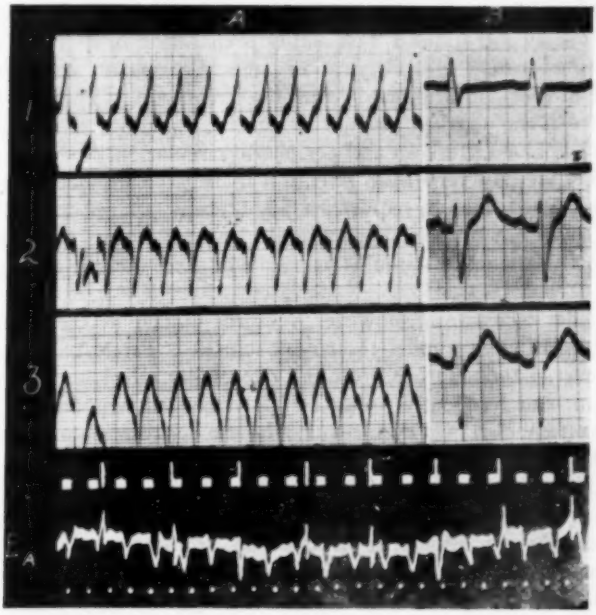

FIG. 6. An example of the value of esophageal leads in definitely establishing the type of arrhythmia. B. Illustrates the normal pattern in the standard leads. A. The tachycardia which developed would be difficult to diagnose without the esophageal lead shown on the bottom line (retouched). The P waves are indicated by the lines above the tracing and the QRS complexes by the squares. (Published by permission of American Heart Journal.)

arises before therapy is started. One advantage of this is that we do not have to deal with the abnormalities of the T waves produced by digitalis.

The same rationale is used with quinidine and Pronestyl. Whereas formerly, for prophylactic effect, we used quinidine, Pronestyl or procaine hydrochloride in patients undergoing cardiac catheterization or cardiac surgery, we have been unconvinced that they offer protection against mechanical stimulation of the ventricles, and since they are depressing to the myocardium we prefer to withhold administration until a specific situation arises.

During operative procedures it is always important to be sure that the patient is adequately oxygenated; the first requirement for handling sinus

tachycardia or sinus bradycardia is to be sure the patient is receiving optimal concentrations of oxygen. Following this, prostigmine or Tensilon (a new anti-cholinesterase agent) may be helpful in controlling tachycardia, and atropine sulfate may increase the rate of a sinus bradycardia or the bradycardia of auricular fibrillation controlled by digitalis. Anesthesiologists have many tricks of their own in handling these arrhythmias by varying the concentration and character of the anesthetic mixture.

Paroxysmal auricular fibrillation and auricular flutter may sometimes be converted by intravenous Pronestyl; or it may be best, in the undigitalized patient, to use an intravenous, fast acting preparation of digitalis to control the ventricular rate. Other types of supraventricular arrhythmias frequently are of short duration and require no treatment. This is particularly true if there is no marked change in cardiac function, as manifested by changes in the blood pressure and peripheral circulation.

Likewise, we pay very little attention to isolated premature ventricular contractions, which seldom require specific therapy. Even when they occur in runs as the result of mechanical stimulation of the heart they usually disappear shortly after the stimulus is removed and do not require specific therapy.

Ventricular tachycardia, however, requires immediate treatment and the probable drug of choice under the circumstances is Pronestyl.[3, 5] Pronestyl does, however, have a rather profound depressing effect on the ventricular myocardium, and frequently produces fairly marked hypotension on rapid, intravenous use which may even require the use of pressor amines to counteract the fall in blood pressure. Pronestyl is not without danger, especially in the presence of complete heart block.[6, 7] While quinidine may be used intravenously, it also has serious toxic effects if too rapidly administered, and is probably more difficult to handle than Pronestyl.

Ventricular fibrillation requires immediate treatment and, with the chest open, cardiac massage is required to maintain temporary circulation.[8, 9] This will rarely terminate spontaneously, and it is usually necessary to "defibrillate" the ventricles by passing 60 cycle current through the heart for brief periods. This is accomplished by inserting metal plates on opposite sides of the ventricles and briefly "shocking" the heart, which produces a state of asystole, or complete relaxation. With further massage the heart may again begin to beat spontaneously, particularly if epinephrine is injected directly into the heart. Kay and Blalock [10] use calcium chloride injected directly into the ventricular cavity, if there is difficulty in establishing rhythmicity.

Ventricular asystole or sudden cardiac arrest requires immediate treatment, similar to that indicated above with the exception that defibrillation is not indicated if the electrocardiogram does not show the presence of ventricular fibrillation.

Heparin may be of value to prevent sludging of blood, and a slight Trendelenburg position seems to promote circulation to the brain—the tissue

most sensitive to deprivation of oxygen—and also to increase venous return to the heart.

In the case of operations upon the heart, the organ is usually easily accessible for direct massage and defibrillation, but it should be pointed out that it is possible to defibrillate through the chest wall,[11] and also to produce rhythmic stimulation and contraction of the heart by electrodes on the outside of the body.[12] One can envision in the near future the possibility of defibrillation of the heart without the necessity of opening the chest, and then using a rhythmic pace maker, possibly with the same electrodes in the esophagus which are used for recording esophageal electrocardiograms. If the nature of the arrhythmia is recognized immediately from monitoring of the electrocardiogram, it seems possible that this might be accomplished by the anesthetist in less time than is required for the surgeon to open the chest for cardiac massage in those cases where the heart is not immediately accessible.

Summary

The types of abnormal cardiac rhythms which may occur during surgery of the heart have been briefly reviewed. It has been pointed out that the proper therapy of these conditions requires that the following be immediately available: oxygen; a means of monitoring the electrocardiogram; certain specific drugs; defibrillation apparatus; a rhythmic stimulator, and a trained team ready to go into instant, premeditated action.

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CASE REPORTS

DEATH FOLLOWING PHENYLBUTAZONE (BUTAZOLIDIN) THERAPY: REPORT OF A CASE*

By David A. Nathan, M.D., F.A.C.P., Marvin L. Meitus, M.D., Lewis Capland, M.D., and Maurice Lev, M.D., *Miami Beach, Florida*

Various undesirable effects have been reported following the use of phenylbutazone (Butazolidin) in the therapy of arthritis and allied rheumatic disorders. Since the initial American clinical evaluation by Kuzell, Schaffarzick, Brown and Mankle,[1] the medical literature is gradually acquiring more and more case histories of heretofore undescribed reactions as well as previously experienced characteristic toxic manifestations due to this compound. First synthesized by the chemists of J. R. Geigy, S. A., of Basle, Switzerland, phenylbutazone (3, 5-dioxo-1, 2-diphenyl-4 n-butyl pyrazolidin sodium) is a synthetic derivative of pyrazol. Aminopyrine (Pyramidon) has the chemical formula 1-phenyl-2, 3-dimethyl-4-dimethylamino-5 pyrazolone, thus indicating a definite relationship between the two drugs.

Although used in several thousand patients with a large percentage of favorable results from a therapeutic standpoint, phenylbutazone has produced the following toxic manifestations: skin rash, edema, nausea, reactivation of peptic ulcer, anemia, leukopenia, stomatitis, vertigo, nervousness, purpura, gastrointestinal hemorrhage, euphoria, hematuria, thrombocytopenia, insomnia, salivary gland swelling, blurred vision, agranulocytosis and hemoptysis.[2] More recently, two fatalities due to agranulocytosis following the use of phenylbutazone therapy have been reported.[3, 4] Arrest of maturation of the granulocytes was believed to be the major factor in causing death in these two patients, and the manner in which phenylbutazone accomplished this was compared to that of its chemical ally, aminopyrine. The fatal outcome in our patient was due to an overwhelming toxic and possibly hypersensitivity reaction, manifested in the skin and viscera.

Case Report

A 60 year old white married woman had been suffering pain from generalized arthritis for many years, with no beneficial results from various types of therapy. Approximately 19 days prior to admission to the hospital she was placed on 200 mg. of phenylbutazone four times a day. At this time the red blood cell count was 4,250,000, the hemoglobin level was 13.40 gm., and the white blood cell count was 8,600. with a normal differential. No abnormal cells were seen in the peripheral blood smear.

Two days prior to admission, although her arthritic pain had subsided, she complained of malaise, weakness, lethargy, mild anorexia and enlarged lymph glands in the anterior and posterior auricular area. Phenylbutazone therapy was discon-

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From the Departments of Medicine and Pathology of The Mount Sinai Hospital of Greater Miami, Miami Beach, Florida.

tinued, but the symptoms grew progressively worse and a diffuse erythema developed over the hands and forearms. On the day of admission to the hospital, February 4, 1953, the patient was acutely ill, complaining of difficulty in swallowing, malaise, anorexia and generalized discomfort.

A past history of sensitivity to codeine and paraphenylenediamine was elicited, but otherwise a review of systems was essentially negative, except for the known severe generalized arthritis of several months' duration.

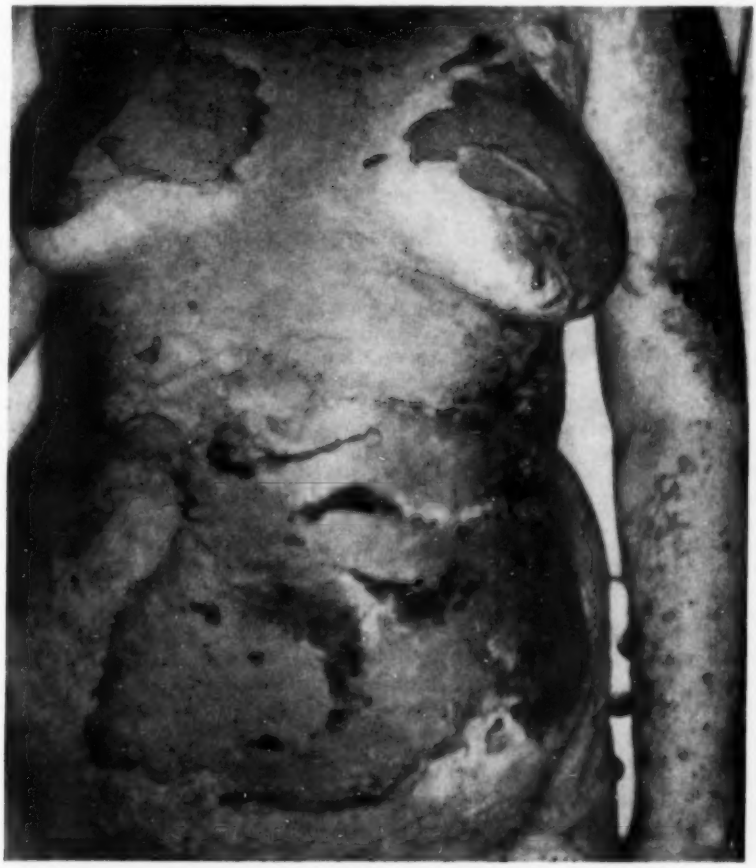

FIG. 1. Urticaria, bullae and denuded areas on trunk and arms of patient who had received phenylbutazone.

Physical examination revealed a blood pressure of 140/85 mm. of Hg, a pulse of 90, and a temperature of 101° F. rectally. A generalized multiform eruption was present, manifested by urticarial lesions, annular urticarial areas with central vesicles and bullae, hemorrhagic bullae, and a diffuse erythematous and edematous involvement of the palms and soles. The cervical and auricular lymph nodes were enlarged and slightly tender. There was moderate periorbital edema, with mild conjunctivitis

present. Diffuse injection and congestion of the nasopharyngeal mucosa were seen, with petechial hemorrhagic lesions over the tongue, buccal mucosa, soft palate and pharynx. The heart and lungs were within normal limits. The abdomen was diffusely tender, but the liver, spleen and kidneys were not palpable. Laboratory examination on admission revealed a red blood cell count of 4,250,000; a hemoglobin level of 12.11 gm., and a white blood cell count of 11,300, with 49 per cent polymorphonuclear cells, 33 per cent band cells, 13 per cent lymphocytes, 2 per cent monocytes and 3 per cent eosinophils. The corrected erythrocyte sedimentation rate was 42 mm. per hour, and the hematocrit was 38 per cent.

The patient's hospital course was a fulminating downward one, with evidence of an increased irreversible toxic reaction. All manifestations on the skin became emphasized, with the vesicular lesions becoming bullous, the bullae rupturing to form large denuded and exfoliating areas, and the skin of the hands and feet becoming encased in single large glovelike bullae (figure 1). Terminally, there was a severe corneal and conjunctival sensitivity reaction, with slough of the entire corneal epithelium bilaterally. In spite of all modes of therapy, consisting of penicillin, vitamins, antihistamines, ACTH, potassium chloride and intravenous fluids, the patient became progressively more toxic. Her temperature varied between 100° F. and 104.8° F. rectally. According to Dr. Albert Hemming, of Geigy Pharmaceuticals, it is likely that the plasma level was 100 mg. per liter during the period of drug administration.[5] Phenylbutazone is metabolized at a rate of 10 to 40 per cent per day, though in most subjects the range is from 15 to 25 per cent per day.[6] A plasma value of 15 mg. per liter was obtained eight days after discontinuance of therapy.* This indicates that the drug was being metabolized at a normal rate and that the patient had been rid of most of the drug. During the 24 hours prior to death, urinary excretion was 500 c.c., and the CO_2 combining power was 27 vol. per cent. The patient died on February 14, 1953, 11 days after admission, in terminal coma and acidosis. During hospitalization, complete blood counts were taken daily, the lowest red blood cell count being 3,700,000, and the lowest hemoglobin level 10.75 gm. The lowest white blood cell count, on February 6, was 7,400, with 45 per cent polymorphonuclear cells, 39 per cent band type cells, 11 per cent lymphocytes, 4 per cent monocytes and 1 per cent eosinophils. Although granulocytes were always adequate, toxic changes in the marrow were evidenced by the presence of progressively increasing amounts of toxic granulations in the white blood cells. Metamyelocytes in the peripheral blood were first seen on the fifth hospital day, and increased from approximately 8 per cent to 15 per cent terminally. The day before death the total protein was 6.4 gm. per cent, the red blood cells were 4,100,000, with 12.80 gm. of hemoglobin, the white blood cells were 9,200, with 30 per cent polymorphonuclear cells, 24 per cent band type cells, 15 per cent metamyelocytes, 25 per cent lymphocytes, 4 per cent monocytes and 2 per cent eosinophils. All white blood cells were filled with toxic granulations.

Postmortem Examination: The pathologic changes were both recent and old. The outstanding recent changes lay in the skin, myocardium, kidneys, lungs, pancreas, adrenals and intestines. The outstanding old changes were found in the spine and in the lungs.

Skin: The gross changes have been described above. Histologically, some sections showed an absence of the epithelial layer, with marked degenerative, necrotic and coagulative changes in the derma. Lymphoid cells and neutrophils were pocketed in the latter. Other sections showed a thick crust of keratinized squamous cells, beneath which regenerating basal cells were present. The subcutaneous fat presented necrotic changes, with an infiltration of lymphoid cells and neutrophils.

Heart: The heart weighed 270 gm. Grossly it presented no change. Histologically, the myocardium and epicardium presented an infiltration of lymphoid cells

* Dr. J. J. Burns undertook the actual plasma determination on this patient, for which we are extremely appreciative.

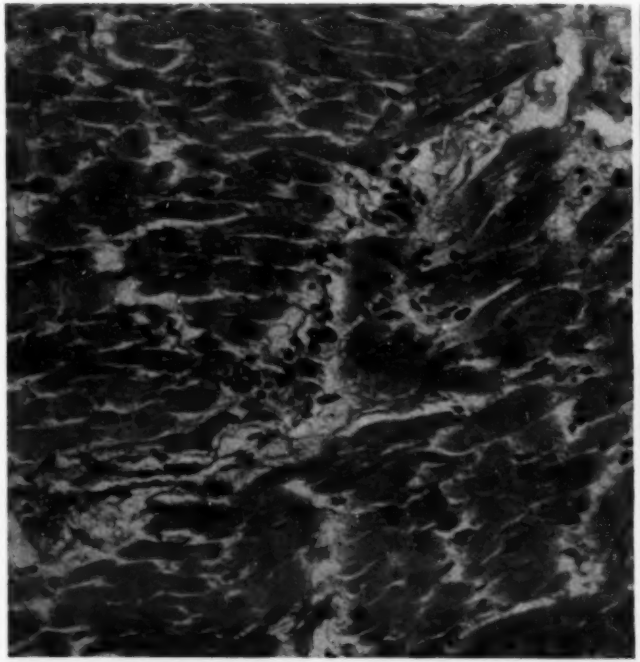

FIG. 2. Histologic section of myocardium, showing nonspecific myocarditis. Hematoxylin-eosin stain × 240.

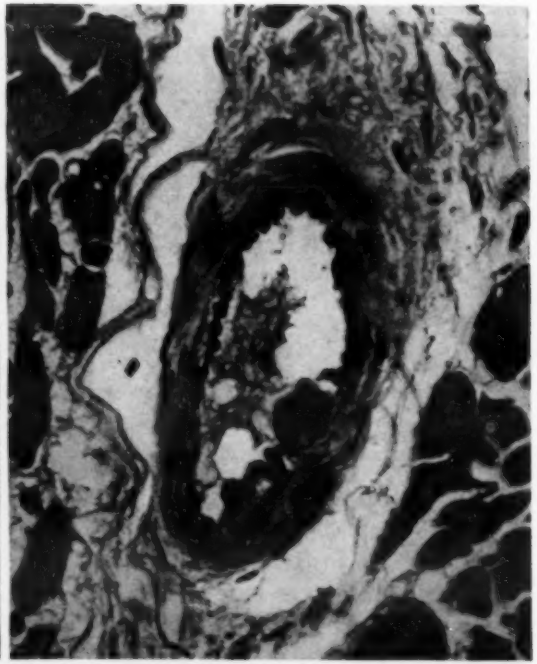

FIG. 3. Histologic section of artery in myocardium, showing degenerative and early necrotic changes. Hematoxylin-eosin stain × 600.

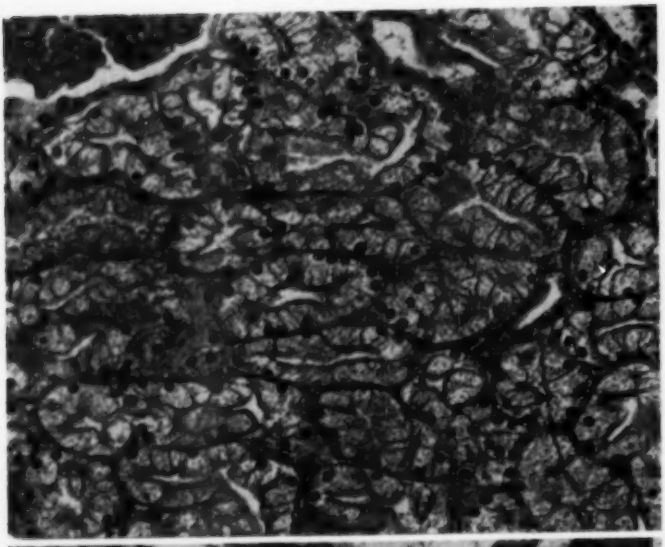

FIG. 5. Histologic section of the kidney, showing hydropic degeneration of the tubules. Hematoxylin-eosin stain × 240.

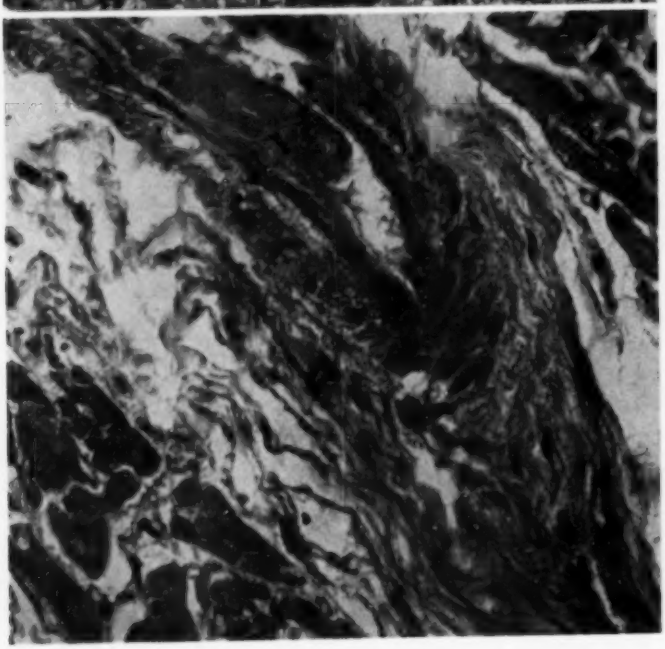

FIG. 4. Histologic section of the myocardium, showing perivascular degeneration of collagen. Hematoxylin-eosin stain × 440.

and scattered macrophages, mostly present around the vessels (figure 2). The arterioles and venules showed degenerative and focal necrotic changes (figure 3). Granular degeneration of collagen (figure 4) was in evidence, with proliferation of fibroblasts.

Kidneys: The organs were large and soft, weighing together 400 gm. The external and cut surfaces were pale and swollen, and the cortex was poorly demarcated from the medulla. Microscopically, the cells of the proximal and distal convoluted

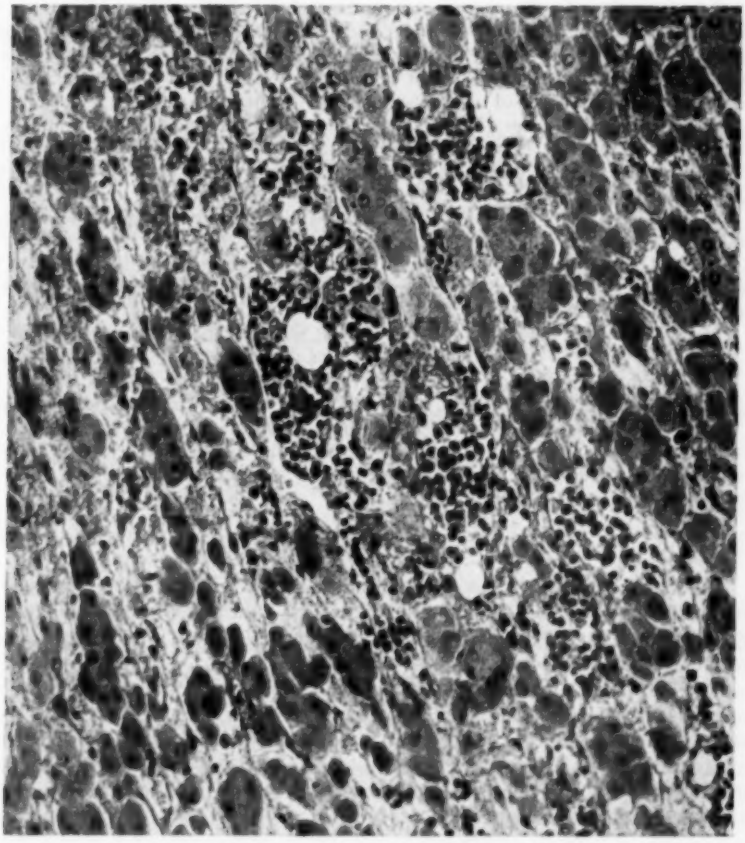

FIG. 6. Histologic section of the adrenal, showing degeneration of cortical cells, with an infiltration of mononuclear cells. Hematoxylin-eosin stain × 240.

tubules were markedly swollen, and their cytoplasm was granular and pale (figure 5). There was a focal infiltration of mononuclear cells in the pelvic lining and in the medulla.

Lungs: The right and left lungs weighed 550 and 450 gm., respectively. The organs were firmer than normal. Histologically, both old and recent pathologic changes were present. The older change consisted of a widening of the alveolar spaces, with a proliferation of collagenous connective tissue in the septal walls. The

recent changes were in the form of focal infiltrations of mononuclear cells, with the presence of either a protein precipitate or fibrinoid material in or lining the alveoli. The bronchi showed exfoliation of mucosal lining cells in many areas, with an infiltration of mononuclear cells in their walls. Masses of bacteria surrounded by mononuclear cells were focally distributed. The arterioles showed swelling of their walls, and some of the venules contained recent thrombi.

Pancreas: The organ was normal grossly. Histologically, there was a focal infiltration of lymphoid cells.

Adrenals: Grossly, these organs showed no change. Microscopically, there was a focal infiltration of lymphoid cells in the cortex and medulla, with degeneration of cortical cells (figure 6). Degenerative changes in the arterioles and venules of the periadrenal fat similar to those found in the myocardium were present, with a dispersion of lymphoid cells and macrophages in the fat itself.

Stomach and Intestines: Grossly, focal areas of hemorrhage were noted in the stomach and jejunum. Histologically, the arterioles and venules showed swelling of elastic tissue and muscle cells, with focal areas of necrosis. A dispersion of mononuclear cells was noted in the lamina propria.

Spine: The fibrocartilage of the intercalated discs showed irregular degeneration and fragmentation, with a focal infiltration of lymphoid cells.

Bone Marrow: Sections were taken from the ribs, sternum and vertebrae. There was an increase in the number of megakaryocytes, with a hyperplasia of both the erythroid and myeloid elements.

Liver: The liver weighed 2150 gm. It was the seat of fatty metamorphosis.

Spleen: The organ weighed 230 gm. It was the seat of acute splenic hyperplasia.

The pathologic diagnosis was: (1) chronic osteoarthritis; (2) exfoliative dermatitis; (3) subacute myocarditis, pancreatitis and adrenalitis; (4) acute vasculitis of the heart, lungs, stomach, intestines and periadrenal fat, with hemorrhages into the stomach and jejunum; (5) pulmonary edema with multiple abscesses; (6) acute nephrosis; (7) fatty metamorphosis of the liver; (8) acute splenic hyperplasia, and (9) pulmonary emphysema with fibrosis.

Comment

The cause of death in our patient is apparently related to the effects of the drug, toxic and possibly hypersensitive, on the skin and viscera. In the case reported by Steinberg, Bohrod and Roodenburg [4] and in our case, the myocardial, vascular and adrenal lesions were prominent. In the former case Aschoff-like bodies were found in the myocardium; in our case a nonspecific myocarditis was in evidence. The vascular degenerative and necrotic lesions present in both cases are reminiscent of some types of hypersensitive reactions seen both clinically and experimentally. Work is being initiated in our laboratories to test the effect of phenylbutazone (Butazolidin) on the myocardium and vascular tissue in the rat.

The mucocutaneous ocular syndrome present in our patient is similar to that previously reported by Charet and Siegel.[7] One may classify this syndrome as an allergic response to a drug simulating erythema multiforme exudativum, which is at the present time considered to be idiopathic in origin. In this case the drug was phenylbutazone.

The literature is replete with reports of toxic effects following phenylbutazone. The incidence of reactions varies from 13 per cent to 44 per cent of patients treated with the drug.[8, 9] In the more severe toxic states, discontinuance of the drug resulted in amelioration of its effects. In our case, in spite of cessation of the drug and the use of counter measures, the patient's clinical

status continued to deteriorate, with ultimate death. The adrenal gland at autopsy showed focal areas of infiltration of lymphoid cells in the cortex and medulla, with degeneration of the cortical cells. This may explain our failure with the use of ACTH stimulation. Cortisone and/or adrenal cortical extract may have been the drugs of choice as substitution therapy for the diseased adrenal gland.

SUMMARY

A death resulting from phenylbutazone (Butazolidin) therapy is reported. The patient died from the toxic and possibly hypersensitive effects of the drug.

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PANHYPOPITUITARISM AND HYPOCALCEMIC TETANY IN A MALE: CASE PRESENTATION *

By J. J. RUPP, M.D., and KARL E. PASCHKIS, M.D., *Philadelphia, Pennsylvania*

LESIONS of the anterior pituitary gland which prevent the elaboration of the pituitary trophic hormones (adrenocorticotropin, thyrotropin and the gonadotropins) will produce hypothyroidism, hypoadrenocorticalism and hypogonadism, the syndrome of severe panhypopituitarism. This syndrome is rare. Ninety-five confirmed cases of severe panhypopituitarism have been collected from the world literature by Sheehan and Summers.[1] In his monograph on extreme insufficiency of the adenohypophysis, Farquharson[2] listed 92 cases collected from the world literature, of which 57 cases presented the typical syndrome.

The following lesions of the pituitary gland have been reported as causes of panhypopituitarism: postpartum necrosis, tumors and cysts, trauma, "spon-

* Received for publication May 20, 1953.
From the Division of Endocrine and Cancer Research, Jefferson Medical College, Philadelphia.

taneous atrophy and fibrosis" and granulomatous lesions such as tuberculosis and syphilis. Only three of the 57 cases reported by Farquharson [2] were caused by spontaneous atrophy and fibrosis of the gland. In view of the rarity of reports of severe panhypopituitarism caused by spontaneous atrophy and fibrosis of the gland, we thought it worth while to report the case of a male who presented the typical syndrome of panhypopituitarism, and in whom autopsy revealed atrophy and fibrosis of the pituitary gland.

Case Report

A 57 year old white unemployed farmer was admitted in February 1949 to the Medical Service for study of the cause of a refractory anemia. He had been well until 1940, when he developed symptoms of prostatism for which a transurethral resection was performed. The operative procedure was tolerated well and was followed by a remission of symptoms. One year later he noticed loss of libido and potentia, decrease in body hair, decrease in appetite, weakness, easy fatigability and intolerance to cold. Between 1941 and 1948 there was a gradual weight loss of 28 pounds. In the fall of 1948 the patient was admitted to another hospital because of bouts of nausea and vomiting. Studies performed during that admission failed to reveal any abnormality except for a severe anemia. Between October and December of 1948 he was given 10 whole blood transfusions and liver extract for the anemia which, however, proved to be refractory.

Physical examination revealed a white male who appeared older than his stated age of 57 years. The patient was neither malnourished nor cachectic. The head hair was normal, but facial, axillary and pubic hair were scant. There were no abnormal eye signs, and the funduscopic examination was normal. Examination of the heart, lungs and abdomen revealed no abnormalities. The skin was dry and not unusually thick. There was no myxedema. Depigmentation of the skin characteristic of vitiligo was present; there was no pigmentation of the buccal mucosa or of the creases of the hands or axillae. The testes were smaller than normal. The neurologic examination was normal.

Various laboratory studies gave the following results: hemoglobin, 65 per cent; red blood cell count, 2,900,000; leukocyte count, 2,900, with 12 per cent eosinophils; platelet count, 98,000. Repeated urinalyses were normal. A specific gravity of 1.026 was reached during a urine concentration test. The values for blood urea nitrogen, urea clearance and phenolsulfonphthalein excretion were within normal limits. Plasma proteins were 7.84 gm. per cent, with an albumin-globulin ratio of 2.7/1. The results of various liver function tests were within normal limits. Repeated stool examinations did not reveal any occult blood. Gastric analysis showed the presence of free hydrochloric acid. Roentgenographic studies of the chest, upper and lower gastrointestinal tracts and skull were normal, as were the oral and intravenous glucose tolerance tests. The basal metabolic rate was minus 35. Serum cholesterol was 231 mg. per 100 ml. of blood. Urinary gonadotropins as determined by the mouse uterine weight method were absent at a level of six mouse units per 24 hours. The urinary excretion of 17-ketosteroids determined by the method of Holtorff and Koch [3] was 0.8 mg. per 24 hours. In the salt deprivation test of Cutler et al.[4] the value for the urinary chlorides was 461 mg. per 100 ml. of urine. The eosinophil count prior to the injection of 0.5 mg. of epinephrine was 575 per cubic millimeter; four hours later it was 515 per cubic millimeter. Perimetric studies of the visual fields were normal.

During the patient's hospitalization the blood pressure varied between 90/60 and 110/70 mm. of Hg, except for the period of the adrenal crisis (see below), when the blood pressure was as low as 50/30 mm. of Hg. After the completion of the

studies, treatment with testosterone propionate, 75 mg. daily by intramuscular injection, was started. The response to treatment was excellent. Appetite improved, a weight gain of seven pounds occurred over a three week period, and the patient was stronger and more alert. At this time the salt deprivation test was repeated in order to determine if part of this improvement was caused by salt retention resulting from testosterone medication. On the second day of the test the patient developed a typical adrenal crisis. He responded to treatment with desoxycorticosterone acetate, adrenal cortical extract, saline and glucose. Although the pulse rate, blood pressure, urinary output and blood sugar had returned to normal, the patient's general condition was not as satisfactory as it had been prior to the adrenal crisis. Three days after the adrenal crisis the patient developed generalized convulsions and carpopedal spasms. At the time of the convulsions the serum calcium was 4.5 mg. per 100 ml., serum phosphorus was 4.1 mg. per 100 ml., and alkaline phosphatase was 3.7 Bodansky units. Convulsions subsided immediately following intravenous injection of calcium gluconate. In spite of continued oral treatment with calcium gluconate the latent tetany, as evidenced by positive Trousseau's and Chvostek's signs and by blood calcium of 7.7 mg. per 100 ml. persisted until death. The patient died suddenly and unexpectedly seven days after the adrenal crisis and four days after the onset of hypocalcemic tetany.

The positive findings at autopsy were limited to the endocrine glands. There was atrophy, but no fibrosis, of the testes, the thyroid gland and the adrenal glands. The parathyroid glands were not identified. The atrophic pituitary gland showed diffuse fibrosis with a moderate amount of lymphocytic infiltration, with the lymphocytes collected in small foci. The gross and histologic findings of the rest of the tissues were normal.

Discussion

This patient presented the signs and symptoms of severe panhypopituitarism: loss of sexual function with atrophy of the testes, loss of body hair, decreased appetite, weight loss, weakness, intolerance to cold, low basal metabolic rate, lethargy, adrenal crisis following salt restriction, and a refractory anemia with eosinophilia. The clinical picture was that of a multiglandular deficiency, and the various laboratory studies confirmed the diagnosis. The low basal metabolic rate pointed to hypofunction of the thyroid gland. The hypofunction of the adrenal glands was reflected in the low 17-ketosteroid excretion, adrenal crisis and positive salt deprivation test. The unusually low 17-ketosteroid excretion also suggested testicular failure, since a part of the urinary 17-ketosteroids is derived from the testicular androgens. The low values of the urinary gonadotropins suggested that pituitary failure was responsible for the testicular atrophy.

A refractory anemia is a frequent occurrence in patients with panhypopituitarism.[5] This anemia may be of such severity as to dominate the clinical picture, causing it to be attributed to the anemia rather than to pituitary deficiency; such was the case in our patient. The cause of the anemia in panhypopituitarism is not known. In patients with pituitary failure the anemia can be corrected in part by testosterone medication, but it is not influenced by thyroid substance.[6] The anemia of hypophysectomized rats can be corrected by cobalt[7] or by an unidentified pituitary factor.[8]

Four days prior to death the patient developed hypocalcemic tetany. As far as we are aware, hypocalcemic tetany has not been described in cases of severe panhypopituitarism. In some cases of panhypopituitarism the parathy-

roid glands have been found to be small and the cellular elements reduced in numbers.[1] These changes probably reflect the decrease in general body weight, rather than the absence of a pituitary factor controlling the function of the parathyroid glands. There is very little evidence to support the hypothesis that the pituitary gland produces a parathyrotropic hormone.[9] According to Sheehan and Summers, blood calcium levels in cases of panhypopituitarism are normal.[1] Blood calcium values were normal in five other cases of panhypopituitarism observed by the present authors. Neither the cause nor the mechanism of the hypocalcemic tetany which occurred in this patient is known. Although the parathyroid glands were not identified at autopsy, these glands probably were present and functioning normally until a few days prior to death, since the patient had no symptoms suggestive of hypocalcemia until after the adrenal crisis.

The cause of the pituitary fibrosis found in our case is not known. There was no history and no evidence of preceding trauma, no granulomatous lesions, or history of severe blood loss and shock such as occurs in patients who develop postpartum necrosis of the pituitary gland. The histologic picture of the pituitary was that described as spontaneous atrophy and fibrosis.

Summary

A case is presented of panhypopituitarism in a male resulting from spontaneous atrophy and fibrosis of the gland. In addition to the manifestations of hypofunction of the thyroid gland, the adrenal glands and testes, the patient developed hypocalcemic tetany. The cause of neither the pituitary fibrosis nor the hypocalcemia could be determined.

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PAROXYSMAL NOCTURNAL HEMOGLOBINURIA: REPORT OF A CASE COMPLICATED BY AN AREGENERATIVE (APLASTIC) CRISIS*

By WILLIAM H. CROSBY, Lt. Col., MC, USA, *Washington, D. C.*

PAROXYSMAL nocturnal hemoglobinuria (PNH) is an uncommon disease, but not so rare as has been supposed. At least 164 case reports have appeared in print, 28 of them since January, 1950.† PNH is manifested by a chronic hemolytic disease that becomes more active when the patient sleeps. During a hemolytic crisis of moderate intensity the destruction of red cells during sleep may result in "nocturnal" hemoglobinuria that disappears shortly after the patient has been awake for several hours. During severe crises hemoglobinuria may persist day and night. In the absence of crises the patient with PNH may live for years with no hemoglobinuria; sleeping still increases his plasma hemoglobin but it does not top the renal threshold. To the dramatic tide of hemolytic activity the disease owes its somewhat inappropriate name. Hemolysis is not the only manifestation of PNH; indeed, it is not the most dangerous. Most of the patients die with venous thrombosis, either of the brain or of the portal system. Before the advent of antibiotics infection was also a common cause of death. It has been suggested that the susceptibility to thrombosis and infection of patients with PNH may be related to a fault of the leukocytes and platelets similar to the abnormality of the red cell which underlies the anemia of this disease.[6]

PNH varies greatly in its severity. The patient who is presented below was severely affected. He demonstrates in a classic fashion the several manifestations of PNH which involve the red cells, the white cells, the platelets and the bone marrow. The case study is of further interest because of the mode of onset of disease, the complication of an aregenerative crisis, the complete autopsy and the study that was made of the patient's large family.

CASE REPORT

The patient was born in 1925 of Dutch and Anglo-Saxon stock, the fourth of 12 siblings. He had always been well and strong, and after the age of 15 he did a man's work on his father's farm. Just prior to his entry into the Army he had donated blood on two occasions to the National Blood Program. He began basic training in February, 1945. In June he was hospitalized for a respiratory infection characterized by fever, malaise, hemoptysis and a 30 pound weight loss (down from 195). After a week he was allowed to go home on furlough. He quickly regained

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From the Department of Hematology, Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington, D. C., and The Medical Service, Brooke Army Hospital, Fort Sam Houston, Texas.

† It was stated in a recent review of the literature that 123 cases had been reported as of January, 1950.[4] One of the 123 (Malmejac et al.) did not deal with PNH. Meanwhile, 12 additional older case reports have been identified.[21-32] One of these, published by Goelet in 1879, probably represents the first report of PNH to be published in the United States. The diagnosis was not made because PNH had not yet been established as an entity. In identifying this and other old case reports with PNH, the total medical history of the patient was consistent with the diagnosis and, in addition, there was described the appearance of pigment in the urine following sleep, or characteristic tests in vitro were found to be positive.

half of the lost weight, but he never regained completely the sense of good health and well being. In July he underwent a left inguinal herniorrhaphy which resulted in partial atrophy of the left testis. The preoperative red cell count was 4.02 million; hemoglobin, 12 gm.; leukocytes, 7,500; urinalysis was negative. The soldier was sent to Europe in September. He developed a chronic respiratory infection with purulent sputum at that time. In March, 1946, he first noted pallor and jaundice of his sclerae. Symptoms of anemia appeared and gradually became worse. In September he suffered an attack of midabdominal pain that lasted 24 hours. He was seen by the unit surgeon but was not hospitalized. During the next three months very dark urine was noted on several occasions. Late in December he developed malaise and pain in the chest. Dizziness progressed to fainting. On January 2, 1947, he was admitted to a military field hospital. The only positive findings on physical examination were extreme pallor and moderate icterus. Hematocrit was 24; icterus index was 45. He was transferred to a general hospital on January 11. The

TABLE I

Clinical Laboratory Data

Date	RBC (millions per cu. mm.)	Hemoglobin (gm./100 ml.)	Hematocrit	WBC (per cu. mm.)	Granulocytes		Platelets (per cu. mm.)	Reticulocytes (per cent RBC)	Bilirubin (mg./100 ml.)
					(per cu. mm.)	(per cent WBC)			
Jan. 11	1.8	5.9	18	3,600	1,900	53	207,000	4.0	1.1
Jan. 20	1.9	6.9	22						
				3,400	2,100	55			
Interval				to	to	to			
				6,500	4,800	75		6–9	1–1.5
Mar. 5	1.3	5.8	17						
Apr. 15	3.1	9.4		7,400	4,100	56			2.0
May 18	0.93	4	12	10,600	6,200	58	97,000	2.5	
June 20	3.6	12.5		4,600	2,500	54			0.8
July 11	2.2	7.5	22	4,150	2,000	48			0.8
July 22	1.5	6	20	4,400					
Aug. 1	4.1	12	36						
Aug. 16	2.3	7	20	2,500	50	2	46,600	0.4	0.8
				1,100	0	0			
Interval				to	to	to			
				2,600	700	20			
Sept. 13	3.4	11	31	4,000	1,080	27			
Sept. 18	2.9	9.5		6,050	4,900	81			

original laboratory work is shown in table 1. On January 16 the patient was given a transfusion of 500 ml. of group O blood. This was followed by a moderate febrile reaction. The next morning the patient's urine was red. The pigment was benzidine positive but there were no red cells. The patient was group A, and the reaction was ascribed to the anti-A antibodies in the transfused group O plasma. The transfusion raised the patient's hematocrit from 18 to 22. Aspirated bone marrow was interpreted to be megaloblastic. During February the patient was treated with liver extract, without benefit. Several complications of his disease occurred. There was a recurrence of severe abdominal pain lasting several days. There were two episodes of severe headache which were not relieved by analgesics. During the second headache, which lasted three days, the patient's sensorium was clouded. On February 20 he developed a purulent discharge from his left ear due to an infection of the skin of the external canal. On February 22 several superficial ulcerations appeared on his left arm, axilla and chest. The cough with purulent sputum which had been present for more than a year persisted. Chest x-ray and gastrointestinal x-rays with barium

meal were negative. During the skin infections and the bouts of pain the leukocyte count did not show any remarkable variation; from January to March it was frequently below 5,000. On March 5 a series of transfusions was begun. By April 15 the patient had received 16 pints of blood. Only the first transfusion was followed by hemoglobinuria. The effect of this quantity of blood on the patient's red cell count was remarkably small. During the transfusions his hemoglobin never went above 12 gm., and at the end of the course it was 9.4 gm. It should be noted that anti-Rh sera were not available to the hospital. The patient later proved to be Rh-negative and he had been immunized against the D antigen, perhaps by these transfusions. On April 16 the patient was evacuated to the United States. During the trip home he had repeated bouts of nocturnal hemoglobinuria. Symptoms of anemia reappeared. He also noted that a bolus of food would often stop with a painful sensation midway down the esophagus. When he arrived in New York on May 13 his hemoglobin was 4 gm. A transfusion precipitated a febrile hemoglobinuric reaction. He was transferred to Brooke Army Hospital. En route to Texas a large hemorrhoid became thrombosed. He was admitted to the Medical Service of Brooke Army Hospital on May 17, 1947.

Examination on admission demonstrated a tall (74 inches), well muscled young man, dolichocephalic, sparsely bearded, with a feminine configuration of the pubic hair line, masculine distribution of fat and no gynecomastia. His skin, nail beds and sclerae were extremely pale and slightly icteric. The tongue was pallid but otherwise normal. There was a small epigastric hernia. There was a large mass of thrombosed hemorrhoids. The left testicle was smaller than the right. The respiratory system was negative. Examination of the cardiovascular system yielded signs of severe anemia. The blood pressure was 128/60 mm. of Hg. The spleen was not palpable; the liver came down to about 2 cm. below the costal margin on full expiration. Neurologic examination was entirely negative.

In addition to the laboratory studies shown in table 1, other tests were carried out. The patient's bone marrow demonstrated a normoblastic hyperplasia. The myeloid series and the megakaryocytes appeared normal. The peripheral blood showed macrocytosis. Morning urine contained hemoglobin, but that collected after noon did not. Hemosiderin was found in the urinary sediment. The plasma was discolored with hemoglobin, more intensely in the morning than at night. A Donath-Landsteiner test for cold hemoglobinuria was negative. The acid hemolysis test performed in the classic manner of Ham [13] was positive, and thereby the diagnosis of PNH was established. Tests of liver function such as prothrombin time, cephalin flocculation, thymol turbidity and albumin-globulin ratio were normal. The gastric juice contained free HCl after histamine, but only 6 units. When this test was performed two months later there was a normal amount of HCl. Results of the osmotic fragility tests are probably invalid because of failure to take into account the presence of hemoglobinemia. The test repeated later was normal.

On May 20, as a result of an error of cross matching, the patient was given two pints of Rh-positive blood. He developed a moderate febrile reaction (101° F.) after the transfusion was completed. Hemoglobinuria did not appear until the next morning. Following this it was demonstrated that the patient was Rh-negative and immunized against the D antigen. The titer of anti-D agglutinin in saline was 1:128. The patient was subsequently given a series of transfusions of compatible blood. without reaction. By June 20 he had received 15 pints of Rh-negative blood. Nocturnal hemoglobinuria occurred from June 9 to June 18. Again between June 27 and June 30 the patient's urine contained hemoglobin both day and night. During this time the level of plasma hemoglobin was always above 100 mg. per 100 ml. During the night it was as high as 200 mg., falling somewhat during the day but never going below the renal threshold. These crises of hemoglobinuria had no pro-

dromal symptoms, and there was no subjective systemic reaction during the period of hemoglobinuria. The blood urea nitrogen remained normal. Urea clearance was 92 per cent of normal. As the crisis subsided after June 30 the patient's urine would become clear during the day. On a July 4 picnic the patient caught cold and developed a purulent infection of the paranasal sinuses. Hemolysis became more intense, with hemoglobinuria 24 hours a day, and the anemia grew worse. During this infection there was no leukocytosis. As the patient's hemoglobinuria became nocturnal again he was placed at night in a Drinker respirator to sleep. The rate of the ma-

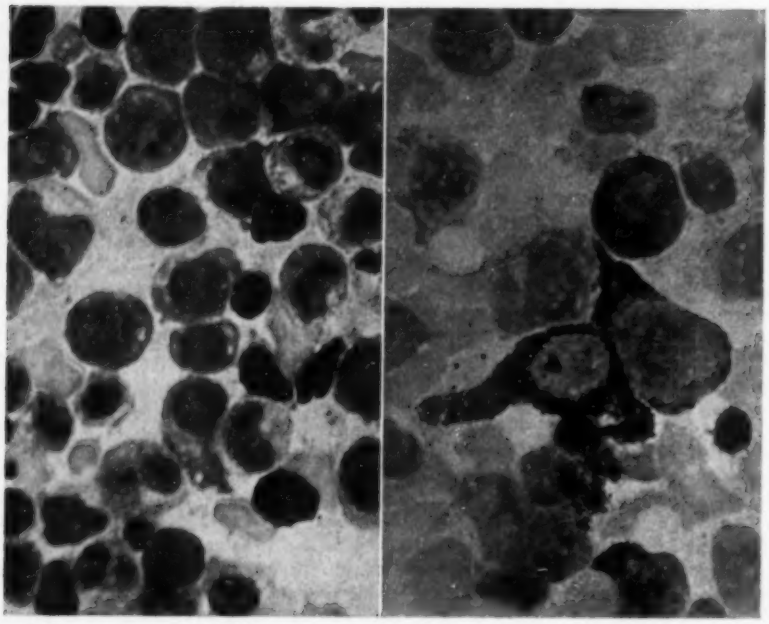

FIG. 1. The panel on the left is the bone marrow of PNH as it is ordinarily seen. There are erythroid hyperplasia and a plentiful number of maturing myelogenous cells. The panel on the right is bone marrow taken on August 22, during the patient's aregenerative crisis. The marrow was generally hypoplastic. The few syncytial masses were composed to a great extent of reticulum cells. Few myelogenous cells had matured beyond the stage of myelocyte. The megakaryocytes were smooth in outline and appeared inactive. Tissue mast cells were prominent. As many as 9 per oil immersion field were found. In the center of the field shown above is a granular, twisted mast cell. There are also several large cells resembling reticulum cells, as well as several lymphocytes, early erythroblasts, and one myelocyte.

chine was set at 20 per minute and the excursion was made deeper than normal. This was done to prevent the damping of respiration that occurs during sleep. Each specimen of urine was saved. Plasma was carefully obtained at 5 a.m. and 5 p.m. each day. The nocturnal pattern of hemolysis continued unaffected by artificial hypernea.

The episode of nocturnal hemoglobinuria spontaneously subsided and ceased on July 23. Because of anemia the patient was given another series of transfusions. He received five pints of blood between July 25 and July 31. Because of an urticarial reaction at the time of the first transfusion he was given 50 mg. of Benadryl each day

before the blood was transfused. On August 1 he left the hospital for a 15 day furlough to his home in Missouri.

On August 15 he returned to the hospital. He had become ill with sore throat and fever on August 12. On August 14 ulcerations appeared in his mouth and throat and pleuritic pain in the left chest. Nocturnal hemoglobinuria recurred. He took some aspirin and this was the only material other than food that he took while he was away from the hospital. On re-admission his temperature was 101° F. There were large dirty ulcers on the buccal and pharyngeal mucosa. Bullae filled with clear fluid were present on his face and torso. He complained of pleuritic pain and pain of similar quality in the left flexor digitorum. His spleen was palpated for the first time but was not very large. The leukocyte count was low, and granulocytes were virtually absent (table 1). The platelet count was also low, although bleeding and clotting times were normal. The reticulocyte count was low. Aspirated bone marrow was hypoplastic (figure 1). The few syncytial masses were composed largely of reticulum cells. Within the masses was a notable number of tissue mast cells, as many as 9 per oil immersion field. Maturing erythroblasts were present but the number was greatly reduced below that observed earlier. Megakaryocytes were present, but there was no fragmentation of cytoplasm and there were no platelets surrounding the cells. Outstanding was the almost complete absence of maturing neutrophilic polymorphonuclear leukocytes. Maturation appeared to be arrested at the myelocyte stage. Maturing and matured eosinophils and basophils were present as usual. The over-all impression was that of an aregenerative reaction. The patient was given penicillin and codeine. For 10 days he was given a daily transfusion of whole blood. He developed a chill after each. On August 18 a course of Pentnucleotide was started. Each injection caused nausea and vomiting. To prevent this, 20 minutes prior to each injection the patient was given subcutaneously 0.5 ml. of 1:1,000 solution of epinephrine. It was noted that following the epinephrine the patient's hemoglobinemia diminished and his hemoglobinuria ceased. When his clotted blood was allowed to incubate at 37° C. for 24 hours there was little hemolysis. This was in marked contrast to earlier experience with this test of the patient's blood. For 15 days starting August 29 he was given epinephrine every six hours. During this time his red cell count for once did not fall but remained about 3.3 million. Hemolysis continued but at a much diminished rate. Pentnucleotide, given August 18 to 22 and August 29 to September 3, had little if any effect. The absolute leukocyte count was low (table 1). The patient remained febrile and ill. Chest x-rays were negative. The infection of the left flexor digitorum profundus progressed. The arm grew swollen and hard and his left fingers became immobile. On September 6, under brachial plexus block, the fascia of the muscle was split. There was no pus. On September 9 the patient announced that he felt well again and got up. His granulocyte count was still low (164 polys). The next day the bullae on his face became purulent (337 polys). On September 11 there were 560 polys, on September 12, 980, and on September 13, 1,800. The next day the patient complained of "sinus headache." An otolaryngologist found no evidence of disease. On the evening of September 14 the patient complained of feeling ill. Next morning he had a severe headache and vomited. The neurologist suspected a cerebrovascular accident. There was weakness on the left side. The patient became worse and a cerebral decompression was performed September 18. There appeared to be a generalized infarction of the left cerebral hemisphere. The patient died that evening.

Necropsy was performed 10 hours postmortem by Colonel G. J. Matt, MC. The right hemisphere of the brain was infarcted by a venous thrombosis. The thrombus in the right transverse sinus near the jugular junction showed the greatest amount of organization and was apparently the site of origin of a process that had spread into the superior longitudinal sinus and for a short distance in the left transverse sinus.

The walls of the sinuses and many subsidiary veins showed signs of intense vasculitis. In other areas where the process was not so old the vasculitis was less pronounced or absent altogether, although antemortem thrombosis was evident. The vasculitis was believed to be secondary to the thrombosis. The thrombotic process had extended generally into the venous system of the right hemisphere, and much of the cerebral tissue was necrotic. Thrombosis was present in other organs. The lungs, liver, lymph nodes and seminal vesicles were affected. The process in these areas appeared to be more recent than that in brain. In view of the patient's bouts of abdominal pain, evidence of old infarction of the portal system was sought but none was found. There was marked siderosis of the kidneys, as is always the case in PNH. In addition, there was stainable iron in the liver and spleen, which is not encountered in this disease unless there has been extensive transfusion. The spleen weighed 360 gm. and was moderately congested. Phagocytes were increased and there was an unusual abundance of plasma cells. The spleen had no infarctions or thromboses. There were no centers of erythropoiesis. The liver weighed 2,600 gm. The liver sinusoids, especially those near the center of the lobules, were greatly dilated, compressing the parenchymal cells. There was thrombosis of the central veins of the liver. There were no gall-stones. The right kidney weighed 275 gm., the left 325 gm. Except for siderosis they were not remarkable: the kidneys of chronic hemoglobinemia. The bone marrow was hyperplastic. The erythroid and myeloid elements were present in ample numbers. There were 1 to 3 megakaryocytes per high power field. Plasma cells seemed to be increased. The lungs showed thrombosis of many small veins, some recent, some older. In addition, there was evidence of resolving pneumonia. The muscles of the left forearm showed a chronic myositis.

Family Study: Several months after the death of this patient his parents and all 11 siblings were examined; blood counts and the Ham test [13] for PNH were carried out on all of them, with normal results. The family history contributed nothing: a younger brother had been briefly hospitalized for a pulmonary tuberculosis and had recovered; a maternal aunt had died of pemphigus; a paternal uncle had diabetes mellitus. There was no history or evidence of any blood dyscrasia.

Discussion

The cause of PNH is not known but it is probably an acquired rather than a hereditary or congenital disease. It is often difficult to date the onset. Sometimes hemoglobinuria appears in childhood. Sometimes a history of anemia dates from early years, but the onset of severe disease occurs after adolescence. The disease may not appear at all until later life. Most patients describe a gradual encroachment of symptoms of anemia. In the present case the onset appears to be related to a respiratory infection. The patient was in robust health beforehand, a donor of blood. Hematologic studies done a month after the respiratory infection showed anemia. The progression of the disease thereafter was uninterrupted. If we conceive PNH to be a disturbance of the reticuloendothelial system instigated by infection, it is of interest that over 10 per cent of the case reports in the literature speak of antecedent malaria.[6]

Against the possibility that PNH might be a hereditary disease is the family study above. All of the patient's 11 siblings and their parents were free of the disease. In the same vein Dameshek [10] has reported the case of PNH in a girl whose identical twin sister was not affected.*

* The author has recently had the opportunity to examine both twins. Their red cells were tested against 14 grouping sera, and the sisters were found to be of the same blood groups insofar as they were tested: O, CDe/cDE, K/k, Fy(a+), P, Le(a+), MN.

The pathogenesis of the hemolytic crisis in PNH appears to depend primarily upon changes in the plasma. The fundamental defect in PNH is cellular. The abnormal cells are somehow susceptible to the destructive effect of a system of normal plasma factors. Four factors have been implicated, two interdependent hemolytic factors and two inhibitors of hemolytic activity. The antagonism of these plasma factors for each other is of considerable clinical importance. The susceptibility of the red blood cell in a given patient does not vary from day to day to any great extent, but the activity of the plasma hemolytic system may vary tremendously. The degree of activity depends upon the balance that exists between the hemolytic factors on the one hand and their inhibitors on the other.[6] During infections this balance is disturbed in favor of the hemolysins: the hemolysins appear to be increased, while the heat stable inhibitor is diminished. After a plasma transfusion reaction the inhibitors and the hemolysins are both diminished, but the balance is disturbed in favor of the hemolysins and a hemolytic reaction ensues.[6, 8] The same is true of many reactions to various forms of therapy in PNH. Epinephrine, on the other hand, causes inhibition of hemolysis in PNH, as shown above. The effect of epinephrine appears to involve increased activity of the plasma inhibitors. The red cells themselves are not altered. The use of epinephrine as a therapeutic agent in PNH is not recommended. We have found that a single injection produces a damping of hemolysis which may in turn be followed by a hemolytic reaction. Epinephrine also causes increased coagulability of blood, and thrombosis is always a threat in PNH. Indeed, in the present case the use of epinephrine may somehow have conditioned the patient to the development of cerebral thrombosis. Other drugs, such as cortisone and ACTH, which predispose to thrombosis, are also contraindicated in PNH, where they have been known to precipitate severe, even fatal thrombotic accidents.[8]

Acidification of serum greatly increases its activity against PNH red cell in vitro. Several diagnostic tests take advantage of this phenomenon. The phenomenon has also been invoked to explain the clinical observation of increased hemolysis during sleep.[9, 13] During sleep the respiratory center is inhibited and there is a tendency to acidosis due to retention of carbon dioxide. This undoubtedly contributes to the "hemolytic tide," but it is probably not the only mechanism involved. As described above, our patient slept in a mechanical respirator, set to cause him to breathe more deeply, and as rapidly as he did when awake. This artificial washing out of CO_2 did not disturb the pattern of nocturnal hemoglobinuria. Remaining awake and quiet at night does, however, prevent nocturnal hemoglobinuria.[13] The phenomenon of nocturnal hemolysis in this disease requires further study.

Aregenerative crises have been well studied and described in other forms of hemolytic disease, such as hereditary spherocytosis and sickle cell anemia.[18, 20] Although it has undoubtedly occurred in patients with PNH,[15, 16, 17, 19] the reaction has not been pointed out as a complication of this disease. The patient of this report undoubtedly underwent such a crisis, with the classic findings of hypoplastic marrow, reticulocytopenia, granulocytopenia and thrombocytopenia. The tissue mast cells in the bone marrow are characteristic of hypoplasia of the marrow.[2] At the time of the patient's death his marrow was found to have recovered from the hypoplasia. In several respects this patient's course during

the aregenerative crisis was different from that encountered in other hemolytic diseases complicated by this reaction. It lasted longer. In hereditary spherocytosis recovery of the bone marrow is under way by the tenth or twelfth day.[15] Our patient became ill on August 12 or even before, and his recovery did not begin until about September 9. The aregenerative reaction lasted 26 days. The crisis in hereditary spherocytosis or sickle cell anemia is not accompanied by the generalized infections that developed in this patient. In other patients with PNH who have had an aregenerative crisis, infection has occurred with ulcerated throats and generalized sepsis.[15, 16, 17, 19] It has been suggested that the leukocytes of PNH are relatively ineffective insofar as they are susceptible to injury by the same plasma factors that destroy the red cells.[6] When, in addition, the number of leukocytes is reduced by the aregenerative reaction, it is not surprising that the defenses against infection are easily breached. Of the five reported patients who have developed the aregenerative reaction, four died, two of generalized sepsis [15, 19] and two, including our patient, of thrombosis that appeared just as the crisis came to its end.[17] Maier's patient recovered.[16] Patients with hereditary spherocytosis have been known to die during such crises, but they died of severe anemia. One unreported PNH patient is known to have died of severe anemia. His bone marrow was quite hypoplastic.

Acute agranulocytosis due to the aregenerative reaction should be differentiated from the chronic leukopenia that is characteristic of PNH. Even the chronic state is associated with a susceptibility to infection. Of 53 patients known to have died with PNH, 11 died of infection.[6] In the present case the patient suffered a multiplicity of minor infections before he developed agranulocytosis. It is noteworthy that leukocytosis did not accompany these infections.

The abnormal platelets of PNH are not ineffective in the rôle of hemostasis. Thrombocytopenia is the usual finding in PNH, yet hemorrhagic disease is rare and, when it has occurred, was not severe. It would seem that the platelet of PNH tends to enter the coagulation reaction more readily than normal platelets, and a liability of intravascular thrombosis is the consequence. Thrombosis is often a severe complication of PNH. Of the 53 cases known to have died with this disease, 24 died of thrombosis, usually of the brain or the portal system.[6] It has been recommended that patients with severe PNH and all patients during crises should be treated with Dicumarol. This may prevent thrombosis, though it does not prevent the increased hemolysis. In severely anemic patients who are not in crisis, the use of Dicumarol has been accompanied by remissions marked by disappearance of abdominal pains and headaches.[7] Remission of hemolysis has been observed with some relief of anemia.[6, 7, 14] This may be a reflection of the ties that exist between PNH and the coagulation system: the PNH platelet is abnormal, and one of the plasma inhibitors is readily destroyed by thrombin. Destruction of this inhibitor tends to upset the hemolysin-inhibitor balance in favor of increased hemolysis. Protection of the inhibitor by Dicumarol would favor decreased hemolysis.[5, 6]

The findings at necropsy in this patient were characteristic of PNH. There is always siderosis of the kidney, but not of the liver and spleen, unless multiple transfusions have been given, as they were in this case. It appeared that thrombosis began in the venous sinuses of the brain and spread into the veins of the brain. Before death the thrombotic process established itself in the veins of several other organs. This, too, is characteristic of death from thrombosis

in PNH.[1, 12] A review of published reports of necropsy in PNH revealed that thrombosis has been found in one case or another in most of the organs of the body. The portal vein, liver, lungs and brain appeared to be especially susceptible. Spleen and kidney were rarely involved. The heart had never been known to be affected, either clinically or at necropsy, but we have recently learned of a man with PNH who died of myocardial infarction during treatment with one of the steroid hormones. Thrombosis affecting the spinal cord has not been reported. Patients with PNH do not develop thrombotic infarctions of the bone marrow, as do those with sickle cell anemia. It is of interest that thrombosis in PNH occurs almost without exception in the venous system. Pulmonary embolism is rare. It has been mentioned above that the tendency to thrombosis in PNH may be due to an abnormality of the platelets.[6]

The frequent occurrence of thrombosis as a cause of death in PNH has suggested that anticoagulant therapy may be of value during crises.[7] The tendency of the process to spread indicates that such therapy should not be delayed until thrombosis is established.

During crises of PNH it is recommended that three forms of therapy be employed:

1. *Moderate dicumarolization during hemolytic crises.* This should be controlled by repeated determinations of the prothrombin time so that prothrombin activity remains around 15 per cent of normal. Dicumarol probably should not be used during the height of an aregenerative crisis with thrombocytopenia, but it is recommended to be started as the patient begins to recover. Our patient died of thrombosis at that time, and so did Merliss' patient.[17] Because heparin blocks the PNH inhibitory factors its use in this disease is not recommended.[5]

2. *Transfusions of red cells washed with saline* to free them of the factor responsible for precipitating the "plasma transfusion reaction."[5, 11] Patients with PNH are especially prone to develop febrile, hemoglobinuric reactions to transfusions of compatible whole blood due to some component in the plasma.

3. *Penicillin or other antibiotics* as required to control infection.

Drugs such as cortisone, ACTH and epinephrine, that predispose to thrombosis, are contraindicated. Liver injections, vitamin B_{12}, folic acid and iron are useless and have been known to cause hemolytic reactions.[6] Splenectomy is futile and dangerous. The mortality rate for the operation in PNH has been 25 per cent.

It is felt that chronic dicumarolization should be tried in all cases of severe PNH.

Summary

1. A case of severely complicated paroxysmal nocturnal hemoglobinuria is reported. In addition to hemolytic anemia with hemoglobinuria, the patient presented a characteristic leukopenia with a susceptibility to infection. He also had repeated bouts of abdominal pain and headache which may have been related to minor thrombotic accidents. The patient ultimately died of a cerebral thrombosis. The possibility is mentioned that the tendency to thrombosis in PNH may be due to a defect of the platelets.

2. During the course of his chronic illness the patient developed an acute aregenerative reaction of his bone marrow, with depressed formation of red cells, white cells and platelets. Apparently as a consequence of the profound

agranulocytosis, the patient developed multiple severe infections. It is pointed out that in other forms of chronic hemolytic anemia in which the aregenerative reaction has been described, this generalized infection is not encountered. The susceptibility to infection of patients with PNH may be due to a defect of the leukocytes.

3. It is apparent from the autopsy report of this patient that once thrombosis becomes irreversible it not only spreads in the organ of origin (in this case the brain), but also occurs in multiple organs throughout the body.

4. In the light of the findings in this case, the therapy of PNH is discussed.

ACKNOWLEDGMENT

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ANEURYSM OF THE CORONARY ARTERY *

By SALVADOR TRINIDAD, M.D., DAVID M. GRAYZEL, M.D., PAUL RAPOPORT, M.D., *Brooklyn, N. Y.*, and NORMAN LEE, M.D., *New York, N. Y.*

TRUE aneurysm of the coronary arteries is of rare occurrence. Since Bougon [1] described the first case in 1812 there have been 48 reported cases in the literature. It would be repetitious to review all the available cases, as various authors, notably Packard and Wechsler,[2] Scott,[3] Harris [4] and Rigdon and Vandergriff [5] have made exhaustive studies of the literature pertaining to this rare entity. We are, however, reporting another case of a true aneurysm of the left circumflex coronary artery, which would bring to 49 the total number of authentic cases of coronary aneurysm.

* Received for publication May 25, 1953.
From the Departments of Medicine and Pathology of the Jewish Hospital, Brooklyn, N. Y.

Case Report

A 59 year old white male was admitted to the Jewish Hospital of Brooklyn on September 3, 1952, with a chief complaint of precordial pain of three days' duration. For the previous five years he had had intermittent episodes of anterior chest pain, usually coming on after exertion or after eating, and always relieved promptly by nitroglycerin. Three days prior to admission he had been awakened by a squeezing precordial pain, which was relieved by nitroglycerin within 15 minutes. The following morning the pain recurred and was present intermittently all that day. Twenty-four hours before admission the pain became severe and constant. The pain was worse in the recumbent position and was somewhat relieved on sitting or standing. Activity did not change the intensity of the pain. There was never

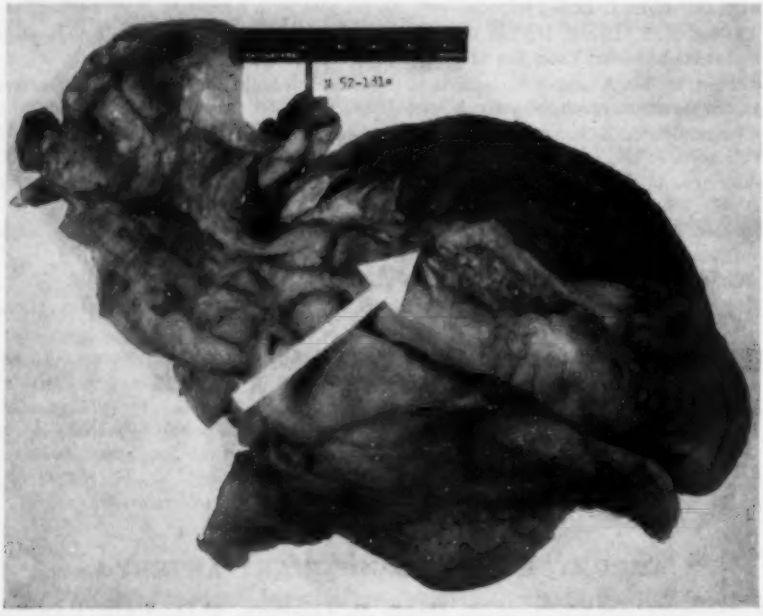

Fig 1. Photograph of heart showing the aneurysm of the coronary artery in situ.

any dyspnea, orthopnea, edema or other associated symptomatology. The patient denied any previous illness, and the family history was noncontributory.

On admission the temperature was 98.6° F., blood pressure was 160/100 mm. of Hg, pulse rate was 108 per minute, and respiratory rate was 20 per minute. The significant physical findings were as follows: The heart sounds were of good quality, and the pulse was regular and strong. The second aortic sound was greater than the second pulmonic sound. No murmurs were audible. There were some fine crepitant râles at both lung bases. The liver was palpable two fingerbreadths below the right costal margin. It was nontender and the edge was smooth. The spleen could not be palpated. There was no edema of the lower extremities.

The laboratory studies revealed the following: hemoglobin, 107 per cent; red blood cells, 5.04 million; white blood cells, 41,600, with 95 per cent polymorpho-

FIG. 2. Photograph of the coronary artery aneurysm.

nuclear leukocytes. The sedimentation rate was 84 mm. per hour. Blood sugar was 183 mg. per 100 c.c. Urea nitrogen was 49 mg./100 c.c. Electrocardiographic examinations showed a typical anteroseptal wall infarction.

The day after admission the patient became cyanotic, dyspneic and restless. The heart sounds at this time were distant and the pulse rate was 148 per minute and very weak. The temperature rose to 103° F., while the blood pressure fell to

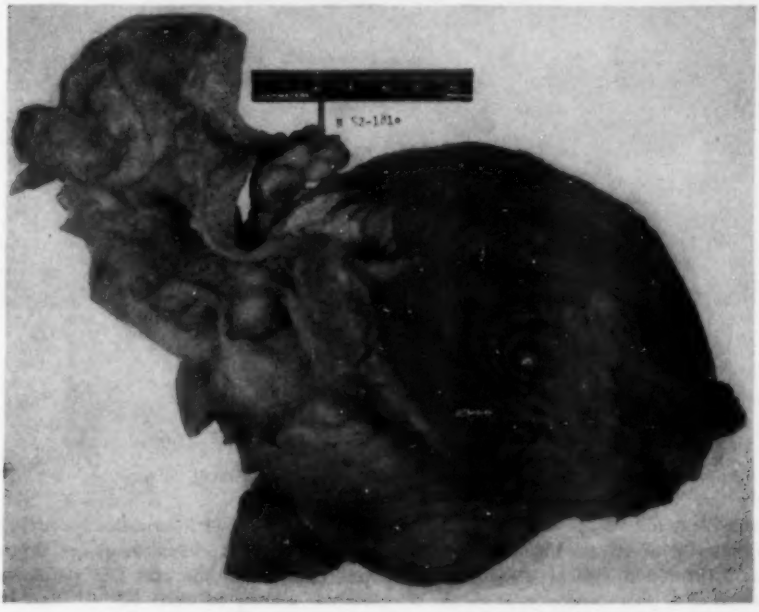

FIG. 3. Photograph of heart showing recent infarct.

90/40 mm. of Hg. On September 6 there was a sudden episode of convulsive movements and gasping respiration which lasted for about half a minute. During this period the pulse rate and blood pressure were unobtainable. An electrocardiogram taken that day showed a ventricular tachycardia with a rate of 125 per minute.

FIG 4. Photograph of aneurysm of abdominal aorta.

From September 6 through September 8 the patient coughed intermittently, bringing up some blood-streaked sputum. An electrocardiographic examination on September 8 showed a typical tracing of an anteroseptal wall infarct. The patient remained in a poor condition, with the temperature spiking between 100° F. and 102° F. until September 14, when he had a sudden convulsive seizure and died.

Morphologic Findings: On postmortem examination the pertinent findings were centered in the heart and great vessels. The heart weighed 550 gm. It was dilated. The pericardium contained the usual amount of a clear, straw-colored fluid. The right atrium was dilated and the auricle was free from thrombi. The tricuspid orifice measured 14.4 cm. and the valves were thin and smooth. The right ventricle was dilated and the wall measured 0.8 cm. in thickness. The pulmonary orifice measured 9 cm. and the valves were not unusual. The left atrium was not remarkable. The mitral orifice measured 12 cm. and the valves were slightly thickened and opaque. The chordae tendineae were thin and delicate and

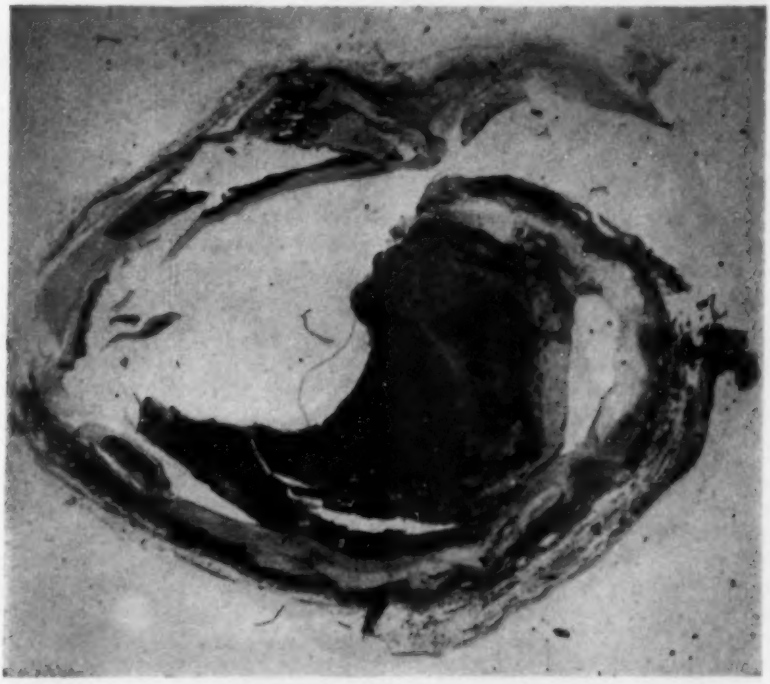

FIG. 5. Photomicrograph under low magnification of coronary artery aneurysm with mural thrombus.

inserted posteriorly. The left ventricle was of the usual size and the wall measured 1.8 cm. in thickness. The aortic orifice measured 9 cm. and the cusps were thickened, slightly deformed and sclerotic. The base of the aorta showed several atheromatous plaques in the intima. The orifice of the right coronary artery appeared partially obstructed by some atheromatous plaques. Beyond the orifice, however, the lumen of the vessel was patent throughout. The intima showed atheromatous changes in its entirety. The left anterior descending artery showed the lumen to be narrowed by sclerotic changes in its wall. About 2 cm. from the origin of the artery the lumen was completely occluded by a thrombus which showed marked adherence to the intima. The myocardium supplied by this artery showed an area

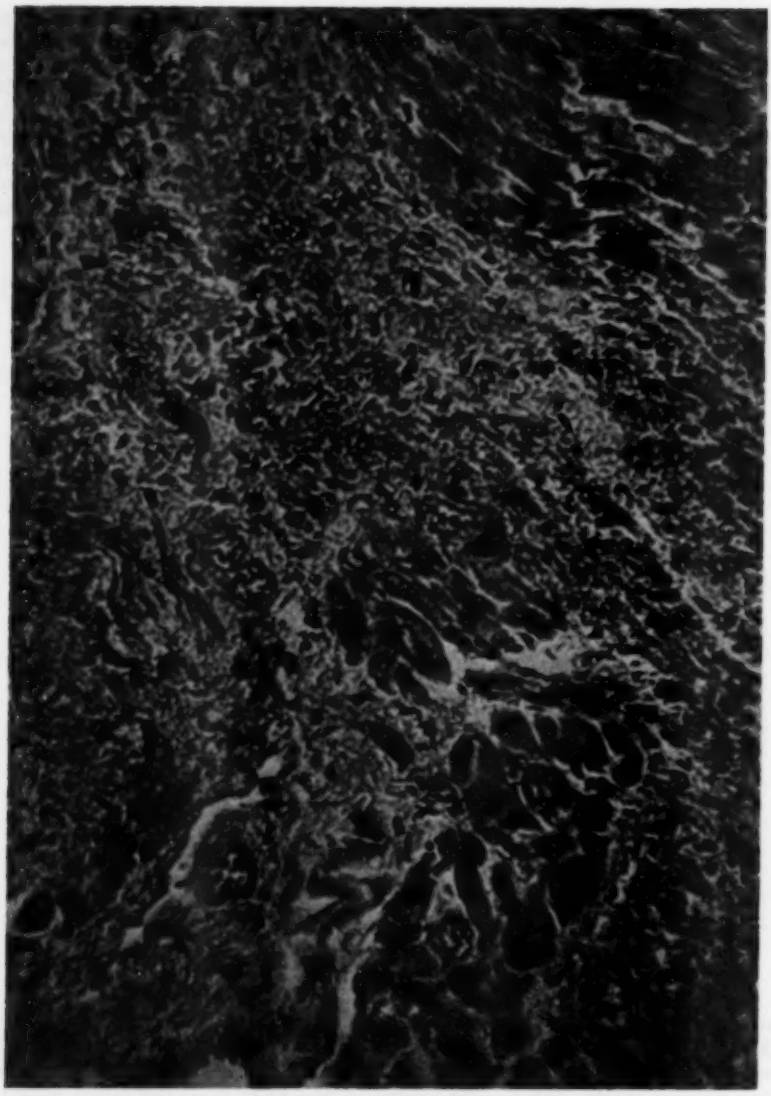

FIG. 6. Photomicrograph of infarct in heart (H&E × 300).

of myomalacia as well as focal areas of fibrosis. The infarction was rather extensive and involved the anteroseptal wall. The orifice of the left circumflex coronary artery was patent and of the usual size. Three centimeters from the point of origin of the vessel there was a fusiform aneurysm which measured 5 by 2 by 2 cm. The wall of the vessel appeared intact throughout. The lumen of this

vessel was obliterated by a laminated thrombus, which was markedly adherent to the intima and showed an area of recanalization measuring 0.5 cm. in diameter. The intima showed only a small atheromatous plaque in one area. The rest of the vessel wall was sclerotic and brittle. The myocardium surrounding the aneurysm was soft and showed an extension of the myomalacia noticed in the anteroseptal wall.

The aorta showed atheromatosis, and in the abdominal portion just before the bifurcation there was another aneurysmal dilatation which measured 6 by 7 cm. The wall was intact but sclerotic. The lumen of the vessel was partially occluded by an organizing thrombus. The intima showed numerous brittle atheromatous plaques.

Microscopically, the coronary artery at the site of the aneurysm showed the wall to be slightly thickened and intact. There was an extensive hyalinization of the media, and at one point the media was markedly altered by irregular areas of calcification. An acicular type of vacuolation was noted in the media, as well as round cell infiltration around capillaries and in the adventitia of the vessel. The elastic lamellae were broken up in places, and the thrombus showed beginning organization around the point of adherence to the intima. The wall of the aortic aneurysm showed also a marked hyalinization of the media, and numerous cholesterol clefts were noted. There were no evidences of an active arteritis in the preparations from the coronary, or from the aortic aneurysms. The rest of the organs showed changes consistent with generalized arteriosclerosis.

Anatomic Diagnosis: Arteriosclerosis, generalized, with particular involvement of coronary vessels, pulmonary artery and branches, aorta, splenic and pancreatic vessels; aneurysms, arteriosclerotic, of the left circumflex coronary artery and the abdominal aorta; thrombus, old and recent, left anterior descending coronary artery; infarct, old and recent, involving the anteroseptal wall of the left ventricle; hypertrophy and dilatation of the heart; congestion of viscera.

Comment

The immediate cause of death in this case was quite obviously coronary thrombosis. What made this case a fascinating one was the incidental finding at autopsy of two separate and distinct aneurysms. One was located in the left circumflex coronary artery and measured 5 by 2 by 2 cm., and the other was in the abdominal aorta and measured 7 by 6 cm. In reviewing the classification of aneurysms of the coronary artery as proposed by Scott,[3] we decided to place our case under the arteriosclerotic type. We do not, however, fully agree that arteriosclerosis per se plays the major rôle in the pathogenesis of aneurysms. If it did, we should see many more aneurysms of this artery.

It has recently been shown that the tensile strength of the musculoelastic arteries, to which the coronary artery belongs, lies chiefly in the adventitia and not in the media. Thus a space-occupying lesion like an arteriosclerotic plaque will tend to protrude into the lumen and to occlude it rather than to cause the vessel wall to bulge outward. However, should the adventitia be injured by hemorrhage or some form of arteritis, then the constant intraluminal pressure will cause the lumen to dilate, particularly if the elastic fibers and the muscle have been destroyed or weakened by the arteriosclerotic process.

There were six cases of aneurysms of the coronary artery reported as being presumably due to arteriosclerosis. The average age for this group was 65 years, which is the age group where one finds extensive and advanced arteriosclerotic changes in the arteries. It is also interesting to note that in none of

the reported cases was the lesion diagnosed ante mortem. The condition, however, is a progressive one and must have been present for a long time.

The type most commonly encountered is the congenital variety. The aneurysms in such cases are due to a congenital failure of fusion of the media at the region of bifurcation of the vessel. These types of aneurysm are similar to the multiple aneurysms one occasionally encounters in the cerebral vessels. Congenital aneurysms are usually multiple in type. A recent report of multiple aneurysms of the coronary artery by Rukstinat [6] is a typical example of the congenital type. His case showed a separate aneurysm of the aorta similar to that previously reported by Monahar.[7] Our case also showed a separate aneurysm of the aorta.

SUMMARY

A case is presented of aneurysm of the left circumflex coronary artery with an accompanying aortic aneurysm, bringing the total cases of true coronary aneurysms up to 49. This case is being classified under the category of the arteriosclerotic type. We believe that injury to the adventitia by hemorrhage or some form of arteritis in addition to arteriosclerosis is necessary for the production of aneurysms. An antemortem diagnosis is practically impossible, as there are no localizing signs or symptoms. Coronary thrombosis is the frequent cause of death in these cases.

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A CASE OF HYPOPLASTIC ANEMIA WITH SECONDARY THROMBOCYTOPENIC PURPURA FOLLOWING THE USE OF CHLORAMPHENICOL * †

By HARRY E. THOMPSON, M.D., F.A.C.P., and HAROLD J. ROWE, M.D.
Tucson, Arizona

THIS is the report of a case of hypoplastic anemia with secondary thrombocytopenia, following the therapeutic use of chloramphenicol. Although a number of cases have appeared in recent literature,[1, 2, 3, 4, 5] this one was deemed to be of more than usual interest and is reported for the following reasons: (1) the immediate, but not complete, control of hemorrhage by the use of concen-

* Chloromycetin.
† Received for publication April 11, 1953.

trated platelet infusion, as described by Minor, Burnett et al.[6]; (2) the temporary palliative effect on the process of ACTH and cortisone; and (3) the ineffectiveness of these and other measures to prevent a fatal termination.

Case Report

The patient, a 48 year old white female, had been in good health until February, 1952, when she complained of the sudden appearance of bruises on her skin during the preceding 10 days, and of a feeling of rapidly increasing generalized malaise.

Her past history revealed several operations, including appendectomy, uterine suspension, hysterectomy, minor operations for thrombotic hemorrhoids and, most recently, a cholecystectomy (December, 1950). All of these were without sequelae. She also had had a recent mild left sciatic syndrome which responded to physiotherapy.

In her present history she stated that she had been well except for occasional colds, of which she had had four or five in the past year. She had had a severe, acute bronchitis in July, 1950, which was thought to be of viral, or coccidioidomycotic origin, and for which she had received approximately 1,000 mg. of chloramphenicol every 24 hours for seven days. She also took 750 mg. of chloramphenicol for three to five days without the advice of a physician with each succeeding upper respiratory infection. Her last upper respiratory infection had been in December, 1951, at which time she took 1,000 mg. of chloramphenicol daily for approximately seven days. She had taken none since.

Physical examination revealed a short, stout white woman in no acute distress. Numerous petechiae were noted over both arms and legs, and a few large purpuric areas were seen over the abdomen. No nose and throat pathology was noted, and the nasal and gingival membranes showed no evidence of hemorrhage. Her tourniquet test was positive.

She was hospitalized on March 7, 1952, and laboratory tests revealed a thrombocyte count of 26,000, with 2,840,000 erythrocytes, 10.2 gm. of hemoglobin, 4,500 leukocytes and a normal differential count. Her clot retraction test was negative in 24 hours. A bone marrow biopsy from the ilium revealed a marrow normally pleomorphic but of diminished cellularity, with a marked decrease in the number of megakaryocytes. No atypical or abnormal cells were seen. There was no fibrous thickening of the marrow reticulum; the marrow picture was considered more characteristic of secondary than of primary thrombocytopenia. The Wassermann test was negative. Quantitative analysis of the urine was negative for mercury, arsenic, lead, and Bence Jones protein. Serum calcium was 10.1 mg. and serum phosphorus 3.7 mg. Alkaline phosphatase was 3.0 Bodansky units, and the total proteins were 5.5, with albumin 3.8 gm. and globulin 1.7 gm. The albumin-globulin ratio was 2.2 to 1. X-rays revealed no intrinsic pathologic process involving the long bones.

The diagnosis of secondary thrombocytopenia with hypoplasia of the bone marrow was made. It was felt that splenectomy was contraindicated, because of the few megakaryocytes in the bone marrow. The source of marrow depression was sought. Exposure to D.D.T. (dichloro-diphenyl-trichloro-ethane) appeared possible, since her house had been treated with these crystals for pest control. There was no proof of ingestion or inhalation of this drug, or of damage from it. There are, however, reports in the literature of such toxic effects.[7] No other chemicals or drugs that might have caused this depression were found.

The patient was given six blood transfusions of 500 c.c. each. The thrombocyte count rose to 42,000, with 3.5 per cent reticulocytes, 14 gm. hemoglobin and 3,000,000 erythrocytes. She was then given 30 mg. of ACTH (adrenocorticotrophic

hormone) intravenously daily for five days, and then started on oral cortisone, 100 mg. daily, in divided dosages of 50 mg. each for one week. This dose was then reduced to 50 mg. daily. Massive doses of iron, B_{12} (Cyanocobalamin), liver extract and vitamins (both parenterally and orally) were given. During the ACTH therapy the patient gained 25 pounds and exhibited a marked euphoric state. Her blood pressure increased, and grade 2 ankle edema appeared. These subsided with the cessation of ACTH therapy. She exhibited no toxic reaction on a maintenance dosage of 50 mg. of oral cortisone daily. She was discharged as improved on March 18, 1952, the erythrocytes numbering 4,420,000 and thrombocytes 40,000.

On March 31, 12 days later, the erythrocyte count, hemoglobin and leukocyte level remained the same. On April 10 the erythrocyte count was 3,480,000, with 12.2 gm. of hemoglobin; leukocytes were 6,100, with 46 segmented and 2 immature polymorphonuclear leukocytes, and 45 lymphocytes; thrombocytes were 30,000; hematocrit determinations were in proportion to the blood count. The patient was transfused with 500 c.c. of whole blood at three different intervals. She had no complaints except for extreme fatigue. The petechiae on the abdomen and extremities were still present. On April 29 the erythrocytes were 2,710,000, with 8.8 gm. of hemoglobin, and the leukocyte count was 2,800. Reticulocytes were 0.75 per cent. Two transfusions of whole blood of 500 c.c. each were given, and the erythrocytes rose to 3,640,000, with 10.2 gm. of hemoglobin. The leukocyte count was 4,800, and thrombocytes were 15,000. A bone marrow biopsy showed absolute diminution of all elements, including megakaryocytes.

On May 18, approximately 10 weeks after the first hospitalization, a marked gingival hemorrhage occurred which did not respond to local therapy. The erythrocytes numbered 2,100,000, with 6 gm. of hemoglobin and a leukocyte count of 2,400. The patient was again hospitalized and given daily transfusions of 1,000 c.c. of whole blood, and ACTH, 20 mg. daily intravenously. The bleeding diminished. At this time there was a parallel between lack of hemorrhage and a high erythrocyte level. Hemorrhage from the gingival tissue gradually ceased, and the patient felt better and was discharged from the hospital.

On June 2, two weeks after her discharge from the hospital, the patient was re-admitted because of vaginal bleeding. Examination revealed a stenotic cervix with an accumulation of blood in the cervical canal. This was evacuated and a cervical biopsy taken. Complete control of hemorrhage was not obtained. Bone marrow taken at this time revealed very few immature elements: the predominant type of cell was the mature neutrophil and the lymphocyte. Rarely a nucleated red cell was seen. Megakaryocytes were rarely seen; there were numerous irregular islands of brownish material, in which numbers of vacuoles were seen. These vacuoles varied considerably in size. In general they were rounded and this suggested fat content. The diagnosis was aplastic bone marrow. Eventually the cervical bleeding was moderately controlled and the patient was discharged from the hospital.

On July 1, three weeks after her last discharge, the patient again exhibited increased bleeding from the cervical stump. She was hospitalized, and the cervix was packed with Oxycel and sutured. At this time the thrombocytes were 21,000 and the erythrocyte count was normal. She was receiving 1,000 c.c. of whole blood three times weekly. A course of BAL and one of colchicine were given on the advice of a consultant, with no improvement.

On this admission a bone marrow biopsy revealed a sparsely cellular marrow made up chiefly of supporting adipose tissue; the islands of hematopoietic tissue were abnormally small and widely separated one from another; numerous large phagocytic cells filled with brown pigment were present; no megakaryocytes were

seen. The diagnosis was marked hypoplasia of the bone marrow. The patient improved somewhat and was discharged with a slight cervical bleeding.

On July 31, 1952, the patient suddenly exhibited a hematuria, with the passage of several small clots, cramping pain over the bladder, and a moderate amount of urgency. She was given 1,000 c.c. of whole blood, and the erythrocyte count at this time was 3,780,000, with 11.7 gm. of hemoglobin; the leukocyte count was 4,300, and there were 12,000 thrombocytes. On August 4 the patient was given a 250 c.c. platelet concentrate infusion prepared according to the instructions of Minor and Burnett.[6] It is notable that the bleeding stopped within four to six hours, and the urine the next day was free of blood cells. However, a week later hematuria again appeared. She was given another 250 c.c. platelet concentrate infusion, and again the bleeding was controlled. At this time the erythrocyte count was 4,480,000, with 14 gm. of hemoglobin. She was receiving 1,500 c.c. of blood at 500 c.c. levels weekly by transfusion. Multiple petechial hemorrhages were still present over both legs, and the tourniquet test remained positive. On August 13 she received 1,000 c.c. of whole blood, and on August 18, while the erythrocyte count was 4,760,000, with 14 gm. of hemoglobin, only 10,000 thrombocytes were present. On September 2 the patient was transfused with 500 c.c. of whole blood and during the transfusion vomited approximately 300 c.c. of thick, glistening, black material that resembled clotted blood. No fresh blood was seen. She had no cough. Subsequent stool examinations were negative for gross blood.

On September 3 gingival bleeding occurred which did not respond to local therapy, and she was hospitalized. The erythrocyte count was 2,820,000. The leukocyte count was 2,800 and there were 7.0 gm. of hemoglobin at this time. She was transfused with 1,000 c.c. of whole blood. On September 8 the erythrocyte count was 3,390,000, with leukocytes of 3,650 and 10.0 gm. of hemoglobin. Thrombocytes numbered 6,000. She complained of a headache (this patient had never had headaches previously) and this was followed by a sensory aphasia, confusion and restlessness. No other definite localizing neurologic signs appeared. The next day the patient was a little improved and clearer mentally. A 250 c.c. infusion of thrombocytes was given, without apparent change in the clinical status. Later the same day she exhibited a dilatation of both pupils and weakness of the right arm, and became comatose; at 2:00 a.m. the next morning she had a mild generalized convulsion and died.

Autopsy Report: Grossly, the body showed scattered petechiae and large bright red hemorrhagic stains in the skin of the chest and abdomen. These were also scattered over the peritoneum and the thoracic mucous membranes. In the base of the brain a laceration of the cerebral cortex was seen in the region of the anterior extremity of the fusiform gyrus on the left. Here the cerebral substance was softened and intensely hemorrhagic. Beneath this laceration the substance of the left temporal lobe was converted, in a localized region, into a mass of coagulated, extravasated blood mixed with brain substance. This mass of coagulum almost fell from a large cavity. The brain tissues of the wall of this cavity were increased in opacity and yellow-tinted (xanthochromic); these tissues also presented numerous scattered regions of petechial and larger hemorrhagic stains. There was a diffuse flattening of the cerebral cortical convolutions, as well as a narrowing of the sulci. This was probably the terminal lesion.

The spleen was regular in shape and moderately enlarged, weighing over 400 gm. The tense splenic capsule was thin, smooth and slate gray. The splenic pulp was slightly and diffusely reddened, but essentially normal in texture and consistency. The Malpighian markings were neither obscured nor abnormally conspicuous.

The size and shape of the kidneys were normal, the thin renal capsules stripping readily from smooth cortical surfaces. There was no dilatation of the renal pelvis, but many calices were lined with mucosa, which was lusterless and dark red. There appeared to have been submucosal hemorrhages.

The suprarenal bodies were regular in size and shape, with normal markings.

The abnormal microscopic findings were most prevalent in sections of the sternal bone marrow, where there was marked decrease in the amount of hematopoietic tissue. The hematopoietic centers of red bone marrow were widely separated, with marked increase in the amount of supporting adipose tissue. The hematopoietic islands were diminished in cellularity but the tissue was pleomorphic. A rare megakaryocyte could be found. There was no fibrosis, and no infiltration with foreign cells. Numerous large stellate reticuloendothelial cells containing brown pigment were seen. These findings were thought to be indicative of a hypoplastic type of aplastic anemia with thrombocytopenia and purpura.

Summary and Conclusions

A fatal case is presented of a hypoplastic type of aplastic anemia with thrombocytopenia and purpura following the intermittent use of chloramphenicol over a two year period. This medication was utilized for only short periods of from three to seven days, and probably on no more than six occasions. The predominating symptomatology was due to hemorrhage, which appeared in the subcutaneous tissues, nasal mucosa, gingivae, urinary system, cervix and, finally, in the brain. Treatment consisted of infusions of whole blood and of thrombocytes and ACTH, cortisone, BAL, colchicine, massive doses of B_{12} and liver extract, and symptomatic measures. While undoubtedly these agents served to prolong life, the depression of the bone marrow persisted and the patient succumbed eight months after the onset.

It appears that chloramphenicol, in relatively small and intermittent dosages, is capable of producing marked and apparently irreversible changes in the hematopoietic system of a susceptible individual.

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CORTISONE TREATMENT OF SUBACUTE NONSUPPURATIVE THYROIDITIS: REPORT OF TWO CASES*

By Julius Kahn, M.D., F.A.C.P., Ramon J. Spritzler, M.D., and Walter E. Shector, M.D., *Los Angeles, California*

Acute and subacute nonsuppurative thyroiditis is a disease of unknown etiology which usually involves the entire gland in an inflammatory reaction.

The causes are probably numerous. The disease commonly is preceded by an acute upper respiratory infection. Some of the reported cases have followed specific infections about the nose and throat, and others have followed specific general diseases varying from measles to rheumatic fever. Suppuration occurs rarely; when present it is unusually due to the common pyogenic organisms. It is the opinion of most observers that the cause or causes of the acute and subacute nonsuppurative varieties are unknown.

The pathology during the acute stages consists of perivascular polymorphonuclear and small round cell infiltration and edema. In the subacute stage a predominance of round cells occurs, along with pseudotubercles containing giant cells which appear to phagocytize the colloid.[1]

The clinical picture is characterized by an acute or subacute onset with fever, often chills, and pain in the neck, aggravated by swallowing. In many instances, there has been a preceding respiratory infection. The thyroid gland is found tender and swollen. The involvement may be confined to one lobe at the onset, but before the disease has run its course the entire gland is involved. The severity of the above picture may vary but more often the course is of moderate intensity.

The white blood cell count is usually moderately elevated and the erythrocyte sedimentation rate is increased. The cholesterol level is usually unaltered. The basal metabolic rate at times may be moderately elevated. The blood protein-bound iodine is often moderately elevated, due supposedly to the destruction and freeing of stored colloid, while the uptake of iodine is usually depressed, due, it is believed, to the functional depression of the glandular cells as a result of the disease process.[2] Needle biopsy studies, as pointed out by Crile, permit one to make a diagnosis in the doubtful cases.[3]

The course of the disease is self-limited as a rule, and the duration usually a matter of weeks, though individual instances of unusually short and long durations with no permanent impairment of thyroid function are seen.

In recent times the most effective treatment has been x-ray radiation, with a

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total of approximately 800 roentgens administered over a period of a week.[1] Symptoms and signs usually subside in the course of two weeks with no overall functional disturbance of the gland, though occasional cases are resistant to this therapy and a somewhat larger proportion require repetition of the course of treatment.

We wish to report two cases of acute thyroiditis of the nonsuppurative variety promptly and successfully terminated with the use of cortisone. Case 1 had received roentgen therapy with little effect upon the disease.

Case Reports

Case 1. The patient, a 43 year old white married woman, a native of Pennsylvania, was admitted to the Cedars of Lebanon Hospital, Los Angeles, on June 14, 1950. She had suffered an acute upper respiratory infection accompanied by a sore throat and a cough during the three preceding weeks. Chills and a fever up to 101° F. had immediately preceded her admission to the hospital.

Previous illnesses included a history of seasonal hay fever and asthma when in the East. Rheumatoid arthritis was said to have caused confinement to bed over a period of years about 10 years earlier. However, the description of this illness suggested a profound psychoneurosis rather than rheumatic disease. Hysterectomy had been performed 10 years before for a painful endometriosis.

Examination on admission revealed a temperature of 100.5° F., a pulse rate of 120 per minute, respirations of 14 per minute, and a blood pressure of 130/80 mm. of Hg. The face was flushed and the patient had a frequent and hacking cough. The anterior nasal sinuses were normally translucent and the throat was not significantly altered. Sibilant râles were scattered throughout both lungs. The heart was hyperactive but manifested no murmurs. Striking tenderness of the right lobe was noted on palpation of the thyroid gland. The rest of the physical findings were not abnormal. The blood count was normal except for a white blood cell count of 14,700, with 77 per cent polymorphonuclear cells. Chest x-ray and urine were normal.

A diagnosis of acute thyroiditis and allergic bronchitis was made.

The patient was started on chloramphenicol and between June 14 and June 18 received approximately 6.5 gm. On June 15 both thyroid lobes were tender and enlarged.

On June 15 the protein-bound iodine was 13.3 micrograms. The radioactive iodine uptake at this time was zero.

Because of the persistence of signs and symptoms, on June 16 the patient was started on roentgen therapy under the direction of Dr. Henry L. Jaffe, and this was continued through June 23, with a dosage of 50_r the first two days and a dosage of 100_r on each succeeding day for a total dosage of 650_r, directed to the thyroid gland anteriorly.

The temperature was normal by June 16, but the rapid pulse and local thyroid findings persisted. On June 23 the gland was less tender and the patient was sent home to await further developments.

On July 3, because of a return of thyroid tenderness and swelling, dysphagia, orthopnea and slight fever (100.6° F., rectal), the patient was readmitted to the hospital. Laboratory studies were normal except for an erythrocyte sedimentation rate of 46 mm. in one hour. The patient was started on 100 mg. of cortisone daily, administered intramuscularly. Within 24 hours the patient felt generally better; she was afebrile and the dysphagia had left. On the fifth day after start of treatment the gland was no longer palpable. The cortisone was continued for seven days, to July 10, when the patient was discharged. At that time she was apparently well except

for a slight unexplained stridor, which subsequently left, and a persistently rapid sedimentation rate. Subsequent observation revealed no return of thyroid symptoms.

Case 2. The patient, a 38 year old white married woman, had been ill approximately two weeks with cough, fever and chills. On April 5, 1952, when her neck became swollen and tender, she sought medical attention.

She had been born in Chicago and, except for frequent sore throats, her childhood was a healthy one. Six weeks prior to the present illness an abscessed tooth had been extracted. Four weeks prior to the present illness she had had severe pain in her right shoulder. She was seen by another physician, who administered x-ray treatment for what was considered to be an acute bursitis.

Examination on April 5 was significant in the following: The temperature was 99° F. The cardiac action was regular, with a rate of 90 per minute. Blood pressure was 130/80 mm. of Hg. The oropharynx and nasal passages were normal in appearance. The thyroid gland was enlarged bilaterally and was very firm and extremely tender. There was no regional lymphadenopathy.

X-ray examination of the chest was normal. The hemogram was normal. Sedimentation rate (Wintrobe) was 52 mm. per hour, corrected.

A diagnosis of acute thyroiditis was made and the patient was given 300,000 units of penicillin by intramuscular injection, and aureomycin, 250 mg. orally every six hours.

For the following 24 hours there was little change. On the night of April 6 her temperature spiked to 104° F. The following day the gland was still very tender and enlarged but her temperature was 98.2° F. She complained of a constant dry hacking cough and soreness over the area of the thyroid gland. She was hospitalized on April 8.

On admission to the hospital penicillin was continued. On April 9 her temperature was normal but the gland was very tender and swollen. Coughing persisted and was a very disturbing feature. The white blood cell count was 9,000 and the differential was normal. The corrected sedimentation rate was 45 mm. per hour. Blood Wassermann test was negative.

The radioactive iodine uptake was 2 per cent. The blood cholesterol was 102 mg. per cent and the blood protein-bound iodine was 8.4 micrograms per cent. Because of the persistence of her symptoms, and in view of the normal temperature and white blood cell count, antibiotic therapy was discontinued and cortisone was given, 25 mg. every four hours by mouth. On April 10, after 24 hours of cortisone therapy, her pain, tenderness and cough had subsided. She felt so well that she insisted upon being discharged. Accordingly, she was released from the hospital on the evening of April 10, having received 150 mg. of cortisone. She was advised to continue cortisone at home in the amount of 100 mg. daily.

Follow-up: The patient was followed by telephone consultation daily. On April 12, she was feeling well and cortisone was tapered off at the rate of 25 mg. daily. She was seen in the office of one of us (R. J. S.) on April 19. At this time the gland was still enlarged but not tender. She was not coughing and there was no neck tenderness. The sedimentation rate was 44 mm. per hour, the basal metabolic rate was minus 10, and cholesterol was 128 mg. per cent.

Unfortunately, the patient moved away from the city soon after, but on May 12 a postal card informed us she was feeling well.

Comment

Case 1 was a typical one of acute nonsuppurative thyroiditis which followed upon an acute respiratory infection. Roentgen therapy as given to a total dosage

of 650, over six days caused some slight reduction in local tenderness, but the symptoms and signs recurred six days after the last dose. As was pointed out by Dr. Henry L. Jaffe, who conducted this phase of the therapy, it was possible that the return of the symptoms and findings represented a reaction to the therapy rather than a recurrence of the original disease process. Inquiry among other roentgenologists and a perusal of several textbooks on the subject fail to reveal the occurrence of an x-ray reaction of the degree this patient manifested with so small a dosage spread over so many days. Whether the reaction at the time of the second admission was due to an exacerbation of the disease, a reaction to the therapy, or a combination of both, the alleviation of symptoms and signs on cortisone therapy was immediate, dramatic and permanent.

In case 2, a patient who also suffered subacute thyroiditis received almost immediate relief from the administration of cortisone by mouth. While penicillin was given concurrently, it is unlikely that this drug influenced the course of disease.

Crile recently reported the treatment of four cases of subacute thyroiditis similarly dramatically relieved by the administration of either ACTH or cortisone.[4] He mentions having observed cases similarly successfully treated with ACTH in the clinic of Dr. Wineblad in Copenhagen. Krupp et al. report a single case of subacute nonsuppurative thyroiditis successfully treated with cortisone.[5] Rowe et al. report one case suffering acute thyroiditis and exophthalmos intermittently treated over a period of a year with ACTH, with good immediate but only fair late response.[6] Details of this case are not given. Three cases promptly relieved by cortisone were recently reported from the University of Chicago Clinics by Clark, Nelsen and Raiman.[7] We are inclined for several reasons to believe that the case recently reported by Traut of thyroiditis developing in the course of cortisone therapy for arthritis was probably not the acute thyroiditis of the type under discussion.[8] The swelling of the gland was "the size of a goose-egg, in the left lobe," and not diffuse and bilateral, as is ultimately the case in most cases of acute nonsuppurative thyroiditis. The radioactive iodine uptake was 35 per cent, on the high side, a state not present in the type of thyroiditis under discussion. The fluctuant state of the swelling that later developed would lead one to suspect a suppurative process which perhaps yielded to the penicillin therapy as well as to the other measures prescribed.

Despite the prompt response of our patients to cortisone therapy it is to be anticipated, from analogous reactions in other conditions, that some patients will require either repeated courses or more prolonged administration of cortisone or ACTH, if this latter drug is chosen.

The mechanism of the relief of symptoms and signs in cases of thyroiditis relieved by cortisone can only be a matter of conjecture. The predominance of an interfollicular inflammatory reaction as the dominant pathologic change would lead one to believe that the anti-inflammatory reaction of the drug was the source of the benefit in this disease entity, rather than any hormone influence on functioning thyroid tissue. The prompt alleviation of symptoms is also a point in favor of this idea. While large doses of cortisone in laboratory animals have been shown to depress thyroid function, evidence such as this does not seem strong enough to permit one to consider hormonal action on the thyroid as a factor in the subsidence of the inflammation in acute and subacute thyroiditis.[8]

SUMMARY

Two cases are reported of diffuse thyroiditis, one acute, the other subacute, promptly relieved by cortisone therapy.

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EDITORIAL

HUMAN TOXOPLASMOSIS

TOXOPLASMA is an obligate intracellular protozoan parasite which is pathogenic for many species of birds and mammals, including man. Although it was first described by Nicolle and Manceaux in 1908 in a North African rodent, the gondi, it was not until 1939 that Wolf, Cowen and Paige brought conclusive proof of its pathogenicity for man in the case of an infant dying of encephalitis. This observation has been abundantly confirmed, and the clinical and pathologic features of the infection in infants have been precisely described (Cowen, Wolf and Paige,[1] Feldman [2]). Some of the earlier reports have been considered in a previous editorial discussion.[3] The clinical manifestations in adult human subjects, on the other hand, have not yet been clearly elucidated. This is partly because these are quite variable and often trivial, and also because of technical difficulties in reaching a conclusive clinical diagnosis.

Toxoplasma is world wide in distribution, and many species of warm blooded animals have been found naturally infected, including dogs, cats, swine, guinea pigs, pigeons and (in all probability) chickens. These animals are also susceptible to experimental inoculation by practically any route, although intracerebral or intraperitoneal injections are usually employed. Laboratory bred mice or hamsters are preferable because they are highly susceptible and free from natural infection. Chick embryos are also susceptible. Infection occurs after oral administration but less regularly. Isolation of the organism by animal inoculation is regarded as essential for a conclusive diagnosis of human infection. Although some strain differences exist, particularly as regards virulence, all strains thus far studied are identical in antigenic structure and in their capacity to infect any susceptible species of animal, and they constitute a single species, *Toxoplasma gondii*.

Toxoplasma may invade any of a great variety of tissue cells, including macrophages, endothelial cells, ependymal and glial (more rarely ganglion) cells of the brain and retina, parenchymal cells of the liver, kidney, lung, spleen, lymph nodes, skeletal and cardiac muscle. They can multiply only within the cells, but they occur free in the necrotic tissue of the lesions or in exudates in active infections. In stained films (Giemsa) the free organisms are slightly crescentic, pointed structures about 5 micra long and 2 micra wide, with pinkish cytoplasm and a purplish nucleus. They multiply by longitudinal fission and may be seen side by side in pairs or small clumps.

[1] Cowen, D., Wolf, A., and Paige, B. H.: Toxoplasmic encephalomyelitis. VI. Clinical diagnosis of infantile or congenital toxoplasmosis: survival beyond infancy, Arch. Neurol. and Psychiat. **48**: 689, 1943.

[2] Feldman, H. A.: The clinical manifestations and laboratory diagnosis of toxoplasmosis, Am. J. Trop. Med. **2**: 420–428, 1953.

[3] Editorial: Toxoplasma infection in man, Ann. Int. Med. **20**: 832–836, 1944.

Although their appearance is fairly distinctive, they sufficiently resemble certain other protozoa to make hazardous a diagnosis based on morphology alone. In this stage the parasites are highly sensitive to unfavorable environmental factors, but no other more resistant stage has thus far been recognized.

The organisms also occur in large dense clumps within greatly distended tissue cells, the "pseudocysts." The cyst wall is believed to be the wall of the host's cell and not formed by the parasite. It is peculiarly resistant and tough, mechanically and chemically, protecting the parasites from humoral antibodies and apparently preventing egress of toxoplasmic products. There is usually no inflammatory reaction around such cysts, which may remain dormant but viable for months or years. It is thought that occasionally such cysts may rupture and their contents excite a severe inflammatory, probably allergic reaction.

Human subjects or animals after infection develop specific neutralizing and complement fixing antibodies in the serum. These appear to be distinct. Cutaneous hypersensitiveness to toxoplasmic antigen also develops. These reactions appear to be highly specific—no overlapping with other species has been discovered. The technic of these reactions has been elaborated by Sabin et al.[4,5] It is not necessary to utilize live animals in ordinary protection tests to demonstrate neutralizing antibody. If live organisms, e.g., from peritoneal exudate of a mouse, are subjected to serum containing neutralizing antibody (in the presence of a labile, complement-like substance occurring in fresh normal serum), they lose their capacity to take up such stains as methylene blue in alkaline solution.

This "dye test" has proved highly specific, it closely parallels direct neutralization tests and is of great practical value. It becomes positive shortly after infection (one to two weeks), usually in a titer of 1:250 or better, occasionally 1:1,000 or even 1:10,000. This may persist for years after evident infection has ceased, usually at a lower titer (1:16 or higher). The complement fixation reaction is slower to appear(a few weeks after infection) and disappears more quickly, although it may persist for several years. It is not an adequate substitute for the dye test.

Obviously a positive dye test does not prove that an existing illness is due to toxoplasma, although it does prove previous infection or contact with the parasite. If, however, an illness is accompanied by a positive dye test in high or rising titer and if the complement fixation reaction is negative or weak at first but becomes strongly positive, this is strong evidence for active toxoplasmosis.

The infection in young infants is acquired in utero. In them the brain and retina are predominantly involved. In the more acute cases there may

[4] Sabin, A. B., and Feldman, H. A.: Dyes as microchemical indicators of a new immunity phenomenon affecting a protozoan parasite (Toxoplasma), Proc. Soc. Exper. Biol. and Med. **108**: 660–663, 1948.

[5] Sabin, A. B.: Complement fixation test in toxoplasmosis and the persistence of the antibody in human beings, Pediatrics **4**: 443–453, 1949.

be fever, convulsions, jaundice, enlargement of the liver and spleen and cutaneous eruptions. Many of the survivors show evidence of focal damage to the brain which is often devastating, with chorioretinitis, hydrocephalus and mental retardation. Roentgenograms of the skull often show small scattered areas of calcification in the brain. In a series of 103 cases studied by Feldman,[2] most of whom had passed the acute stage, 99 per cent had chorioretinitis; 63 per cent, calcifications; 56 per cent, psychomotor retardation (Eichenwald found 80 per cent); half, convulsions; and half, hydrocephalus or microcephalus. Such infants give a strongly positive dye test and (usually only after a month or more) a positive complement fixation test. The mothers give a positive reaction to both tests. As these antibodies may be transferred passively to the fetus, positive reactions in earliest infancy must be interpreted with some caution.

The mothers of these infants, with the rarest exceptions, show no evidence of illness, and subsequent children have not been infected. It has been assumed that these women acquire a symptomless but active infection during pregnancy and transmit the parasites to the fetus through the placental circulation. Confirmatory evidence for this has recently been furnished by Prior et al.,[6] who demonstrated by animal inoculation the presence of toxoplasma in the blood of a healthy young woman, not pregnant, who showed no abnormality except positive serologic and cutaneous reactions.

Inapparent infection is not restricted to pregnant women. Extensive surveys among various segments of the general population with both the intracutaneous test and the dye test indicate that such infection is widespread. Frenkel [7] obtained positive intracutaneous reactions in 10 per cent of young adults and 28 per cent of older hospital patients. Similar figures have been reported by others (Feldman [2]) using the dye test also, and in some groups the positive results have been as high as 50 per cent (Sabin [9]).

But few cases of manifest infection in older children or adults have been conclusively proved by successful animal inoculation. Cases of severe encephalitis have been reported in older children (Sabin [10]) and more rarely in adults.[11, 6] Chorioretinitis appears to be rare. In adults manifestations of generalized visceral involvement appear to be more frequent than neurologic disturbances. Pinkerton and Henderson [12] reported two fatal cases

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[10] Sabin, A. B.: Toxoplasmic encephalitis in children, J. A. M. A. **116**: 801, 1941.

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[12] Pinkerton, H., and Henderson, R. G.: A previously unrecognized disease entity simulating the typhus-spotted fever group, J. A. M. A. **116**: 807, 1941.

with fever, prostration, a macular rash like spotted fever, interstitial pneumonia and involvement of the liver and spleen. Magnusson [13] has observed two similar cases, and Brennan et al.[14] have reported one less acute case, in which the diagnosis was based on serologic reactions only.

Siim [15] in Denmark has reported seven cases of mild febrile infection with coryza, generalized enlargement of the lymph nodes suggesting infectious mononucleosis, but presenting positive dye tests in substantial and rising titer and positive complement fixation tests. In one case he failed to isolate the organism by inoculation of animals with a lymph node, but he is quoted (Feldman [2]) as having succeeded in later attempts.

Accidental infections in the laboratory have been reported in two cases by Ström.[16] One woman of 22, presumably infected per os, had a moderately severe illness with fever, conjunctivitis, a maculopapular eruption, lymphadenitis, and a little later signs of encephalitis, meningitis and myocarditis. Headache, mental exhaustion, inability to concentrate, and petit mal-like seizures were still present six months later. The second case, a woman of 22, three days after pricking her finger with a needle infected with toxoplasma developed mild fever and a swollen tender axillary gland. There was some mild malaise for about one month. In both cases the diagnosis depended upon a positive dye test, the titer rising under observation to a high level. Kass et al.[11] also refer to a case observed by Sexton, Eyles and Dillmare, with fever, a maculopapular eruption, a positive serologic reaction and an acute fatal course. One laboratory worker, following an accident, observed the appearance of a positive serologic reaction with progressive rise in titer without any clinical symptoms whatsoever.

Several cases have been reported with no history suggesting previous toxoplasmosis, in which organisms have been demonstrated morphologically in the tissues at autopsy or biopsy, usually in the form of pseudocysts (e.g., Kean and Grocott,[17] Syverton and Slavin [18]).

Because of the prominence of chorioretinitis in congenital infections, there has been intensive search for evidence of toxoplasmosis in adults with chorioretinitis. Although in some of the earlier studies (e.g., Frenkel [8]) a high incidence of positive serologic reactions was reported, this has not been confirmed by later work.[2, 19] Chorioretinitis has not been a feature

[13] Magnusson, J. H.: Symptoms of toxoplasmosis, Nordisk. Med. **45**: 344–348, 1951. Abst. J. A. M. A. **146**: 1169, 1951.

[14] Brennan, A. J., et al.: A syndrome characterized by generalized cutaneous eruption, chorioretinitis and eosinophilia, probably due to chronic toxoplasma infection, Am. J. Med. **7**: 431–436, 1949.

[15] Siim, J. C.: Acquired toxoplasmosis, J. A. M. A. **147**: 1641–1645, 1951.

[16] Ström, J.: Toxoplasmosis due to laboratory infection in two adults, Acta med. Scandinav. **139**: 244–252, 1951.

[17] Kean, B. H., and Grocott, R. C.: Asymptomatic toxoplasmosis, Am. J. Trop. Med. **27**: 745–748, 1947.

[18] Syverton, J. T., and Slavin, H. B.: Human toxoplasmosis, J. A. M. A. **131**: 957–959, 1946.

[19] Sabin, A. B.; et al.: Present status of clinical manifestations of toxoplasmosis in man, J. A. M. A. **150**: 1063–1069, 1952.

of proved toxoplasmic infection in adults. The strongest evidence to support this association is that of Wilder.[20] In 53 eyes removed from adults because of pain and blindness and showing granulomatous necrotic retinal lesions similar to those in infantile cases, organisms regarded as morphologically identical with toxoplasma were demonstrated. As confirmatory evidence was lacking (except positive serologic reactions in the only three cases available), the identification must be regarded as tentative, but Wilder's illustrations look convincing.

Failure to demonstrate positive serologic reactions would not necessarily exclude toxoplasma as the etiologic agent. Observations in animals indicate that a positive serologic reaction may subside even though pseudocysts remain in the tissues. Pseudocysts have been observed in human retinal lesions in subacute cases.[7] It has been suggested but not proved that rupture of such cysts and liberation of organisms might account for acute exacerbations of the lesions. At present it is believed by most that toxoplasma is not a common cause of chorioretinitis in the adult.

Treatment at present can be suggested only on the basis of animal experiments. The ordinary antibiotics appear to be useless. Sulfadiazine arrests acute experimental infections and prolongs the life of the animals while treatment is continued, but relapse usually follows as soon as this is stopped. Better results have been reported (Eyles[21]) from the use of the antimalarial drug Daraprim, a 2:4-diamino pyrimidine, which cured permanently up to 25 or 35 per cent of the mice. Eyles found that sulfadiazine and Daraprim exerted a synergistic action, in that the minimum effective dose of each was much reduced and up to 60 per cent of the animals were permanently cured. Their effectiveness in eliminating chronic infection has not been demonstrated. It seems unlikely that either drug will notably affect the organisms in the pseudocysts. A safe effective dose for man has not yet been worked out.

The mode of dissemination of the infection has not been demonstrated. Animal reservoirs are abundant. Transmission by biting arthropods has been suggested. In some species like the dog, pulmonary infiltrations and ulcerative lesions of the gastrointestinal mucosa make the sputum and feces possible sources of infection. Cole et al.[22] have recently reported studies of 37 human subjects who had been in contact with pet dogs with active toxoplasmosis. Two of these persons had well marked clinical symptoms of the disease. In all, nine cases gave positive dye tests, seven in significant titer. One of these was the clinically healthy woman already mentioned, from whose blood organisms were twice isolated. During the preceding month she had nursed a sick dog, which had been "fondled like a child in the

[20] Wilder, H. C.: Toxoplasma chorioretinitis in adults, A. M. A. Arch. Ophth. **48**: 127, 1952.

[21] Eyles, D. E.: The present status of the chemotherapy of toxoplasmosis, Am. J. Trop. Med. **2**: 429–444, 1953.

[22] Cole, C. R., Prior, J. A., et al.: Toxoplasmosis. III. Study of families exposed to their toxoplasma-infected pet dogs, A. M. A. Arch. Int. Med. **92**: 308–313, 1953.

household." The evidence for transmission in these cases is striking but not definitely conclusive.

The large number of cases of inapparent infection revealed serologically in contrast with the rarity of those with recognized clinical illness indicates that, as a rule, the adjustment between the parasite and the host is good. The fetus is susceptible, and if the mother acquires an infection during pregnancy, the fetus is liable to infection while the organisms are being disseminated through the blood stream. Since there is a good prospect that acute infections may be successfully treated, further study to facilitate recognition of these cases is indicated. Until the method of dissemination has been demonstrated, prophylactic measures offer little, but these observations provide an additional reason why pet animals should not be handled like children in a household.

P. W. C.

REVIEWS

Physiological Foundations of Neurology and Psychiatry. By ERNST GELLHORN, M.D., Ph.D., Professor of Neurophysiology, University of Minnesota. 556 pages; 15.5 × 24 cm. University of Minnesota Press, Minneapolis. 1953. Price, $8.50.

The problems faced by neurologists and psychiatrists are not only among the most difficult ones confronting investigators today, but also are among the most pressing clinical ignorances. Both the neurologist and psychiatrist are aware of the vast difference that exists between their ability to diagnose and what they can do after a diagnosis has been established. Chronic neurological and mental illness, moreover, pose very grave economic burdens on the community. Consequently, attacks upon these problems are necessary from as many points of view as possible, and at frequent intervals an assessment and integration of the developing knowledge must be made. In the present volume Dr. Gellhorn has attempted the colossal task of integrating what is known of the basic physiology of the neuron and neuronal groups or networks with the factors involved in the problems of nervous and mental disease. Such an effort will be of interest to all workers in these fields, and especially to those acquainted with Dr. Gellhorn's long experience and numerous contributions.

Many problems and functional levels are discussed under six primary groupings:

I. Intrinsic and Extrinsic Factors Regulating Neuronal Activity
II. Contributions to the Physiology and Pathology of Movements
III. The Physiological Basis of Consciousness
IV. Some Aspects of Autonomic Physiology
V. Integrations
VI. Applications (to schizophrenia, shock therapy, carbon dioxide therapy, etc.)

In general, the author has chosen to discuss a wide variety of topics of particular interest to him and tried to find logical places for them in the tableau of organismal activity. The subjects range from the unit analysis of nervous activity to electromyography, convulsions, consciousness, conditioning, autonomic activity and some physiological concepts relating to mental disease and therapy. A particular bias in the direction of the rôle of autonomic control and especially that of the hypothalamus has in some measure detracted from the value of the overall presentation. Despite the not by any means inconsiderable amount of valuable data and thought to be found in the book, a number of important factors appear to have been slighted in favor of the hypothalamic-cortical system and its rôle in neurological and psychiatric processes. For example, recent work relative to the rôle of rhinencephalic structures in emotion and behavior is greatly underplayed. Many of the new findings concerned with function of the hippocampus, fornix, cingular gyrus, amygdala and other associated areas are of the greatest importance not only in our general considerations of emotion and behavior, but also in regard to our understanding of the "autonomic" nervous areas and functions. So much of this work raises new possibilities, that one can no longer comfortably envision the hypothalamus as the answer to the neurophysiological maiden's prayer—most certainly *not* if it is being discussed just in its rôle as an autonomic center. Such centers are too widespread in the central nervous system to allow one of them completely to overshadow all the others, especially those which have been shown to be of the first importance in somato-visceral integration and correlation.

It seems unphysiological to suggest one out of many interrelated neuronal groups as a multi-functional center of far more importance than other associated groups. In the same way, it does not seem completely sound to suppose that the reactions to

various stimuli to which the whole organism is subjected can be interpreted by constant reference to any one center. To be sure, certain things will affect the hypothalamic-cortical relationships, and this is a part of the whole that must be taken into account, but there is no obvious reason for making this particular relationship more important, let us say, in trying to explain the effects of shock therapy, than bulboreticular thalamo-cortical interrelations, or generalized somato-visceral correlations, or changes in permeability of neuronal surfaces, etc, almost ad infinitum.

Lack of space prevents complete discussion of many other problems arising from this type of presentation, such as some questionable views concerning the theory of carbon dioxide therapy, interpretation of results obtained with the oxygen electrode, etc. In contrast to these are some highly stimulating expositions of problems of convulsive activity, consciousness and homeostasis. The entire book is a most provocative one despite its limitations, and will serve physiologists, neurologists, psychiatrists and others as a summary of much of the material now in the forefront of nervous system investigation.

ROBERT G. GRENELL

Inhalation Therapy and Resuscitation. Publication No. 156, American Lecture Series. By MEYER SAKLAD, M.D., Director, Department of Anesthesiology, Rhode Island Hospital, Providence, Rhode Island; edited by JOHN ADRIANI, M.D. 343 pages; 16 × 24 cm. Charles C. Thomas, Publisher, Springfield, Illinois. 1953. Price, $7.50.

Dr. Saklad, in this monograph, leads the reader through the physiological and pathological bases for inhalation therapy and resuscitative procedures into the practical application of this knowledge. The text is easy to read from the standpoints of type size, make-up and writing style. There are numerous charts and graphs designed to clarify the written text, as well as many photographs and line drawings of equipment and therapeutic procedures.

The practical aspects of gas supply, flowmeters, humidifiers, fire hazards and technics and equipment for administration of inhalation therapy are well handled and up-to-date. The section on resuscitation gives prime consideration to the importance of an open airway and the methods of obtaining and maintaining it. This is followed by a description and critique of the various methods of artificial respiration, mouth to mouth, manual and mechanical. Next, there is a discussion of the etiology, prevention and treatment of asphyxia neonatorum, including an evaluation of technics and equipment used currently in its treatment. The book closes with a brief discussion of cardiac resuscitation.

This book's particular value lies in the completeness of its coverage. The bibliography makes up in source material for any omissions in the text. The informed reader might find that the physiological bases for inhalation therapy have been handled in a more lucid manner by other writers and might question the advisability of devoting so much space, relative to its clinical importance, to "oxygen poisoning." This minor criticism should not detract from the worth of this book as a practical manual for medical students, general practitioners and interested specialists.

R. B. D.

Extrasystoles and Allied Arrhythmias. By DAVID SCHERF, M.D., F.A.C.P., Associate Professor of Medicine, New York Medical College, and ADOLF SCHOTT, M.D. (Heidelberg), M.R.C.P., Medical Officer in Charge of the Cardiographic Department, Queen Mary's Hospital for the East End, London. 531 pages; 19 × 25.5 cm. Grune and Stratton, New York. 1953. Price, $15.50.

This unique and amazing volume represents 30 years' study and investigation by the authors on the subject of extrasystole and the numerous aspects which relate

it to other biological problems, physiological as well as clinical. Recent advances in electrocardiography and physiology are masterfully integrated with present knowledge of cardiac impulse initiation and rhythm, so that a "detailed view" of this subject is realized. The group of arrhythmias discussed in this book is defined as "contractions of the whole heart or parts of the heart due to impulses which are abnormal, either regarding their site of origin, ectopic, or their time of occurrence, premature, or both interfering with or replacing a dominant rhythm."

The volume is introduced with a chapter containing basic definitions of extrasystole, premature contractions, ectopic and automatic beats. This is followed with historical survey (a classic in itself) on the development of our concepts about arrhythmias and the art of feeling the pulse, extending from Chinese thought in 500 B. C. to the period of Einthoven's string galvanometer. It is from this point to our present day concepts with which the volume is concerned. The following five chapters deal with a description of the various types of extrasystoles (the more common types; plus return extrasystole, retrograde conducted extrasystole; extrasystoles in groups; A-V block and extrasystole; and multiform extrasystole, the pararrhythmias, coupling of extrasystoles, pulse alternans, flutter, fibrillation and paroxysmal tachycardia). The discussion concerning each entity of a chapter is divided into the nature and disturbance of rhythm, historical and experimental observation, electrocardiographic and clinical observations and a summary. In some instances, because of the compactness of the discussion, it is a distinct advantage to read the summary first as a means of orientation. Following the summary each entity has its own world-wide bibliography.

The discussion of subsequent material is similarly divided. Two interesting chapters on the relationship of extrasystole to the nervous system, drugs and electrolytes are presented. This is followed by a discussion on the physiological aspects of extrasystole and the localization of the site of origin of extrasystole, which while technical is so arranged as to read like a historical novel. One of the most appealing sections is that on the clinical aspects of extrasystole which contains such subjects as the attitude of life insurance companies toward extrasystoles, clinical evaluation and treatment. The final chapter is a review of existing hypotheses and the author's views concerning the mechanism of extrasystole and automatic impulse formation.

This scientific work is presented with unusual clarity. Discussion of controversial issues is complete and proper references included so that interested readers may pursue further their interest. Throughout this factual reporting, the authors do not hesitate to express opinions and offer suggestions on the basic theory of extrasystole. Many of these opinions are documented by their own extensive literature, a product of lifelong experience with their subject.

Never before has such an exhaustive and comprehensive study of extrasystole been presented under one cover. This book is strongly recommended, not only to cardiologists, but also to those engaged in the study of physiological and clinical problems which center around the initiation and propagation of impulses.

F. B.

Milk Pasteurization: Planning, Plant, Operation, and Control. World Health Organization Monograph Series No. 14. By H. D. Kay, C.B.E., Ph.D., D.Sc., F.R.S., J. R. Cuttell, A.M.I. Mech.E., H. S. Hall, B.Sc., A. T. R. Mattick, B.Sc., Ph.D., and A. Rowlands, B.Sc., M.S. 204 pages; 16 × 24 cm. (paperbound). Published jointly by FAO and WHO and issued also as FAO Agricultural Studies No. 23; available in U. S. A. from Columbia University Press, International Documents Service, New York. 1953. Price, $2.50.

This monograph is a presentation of the technical factors involved in the production of pasteurized milk. It obviously has not been prepared for the use of medical

students or instructors and workers in preventive medicine. It is definitely for the use of the technical personnel responsible for the planning, construction, operation and control of pasteurizing plants.

Part I presents an extended definition and brief resume of the background of modern pasteurization. Part II covers rather fully the planning and construction of the dairy building. Complete "Layouts" are described and illustrated. This part gives a description of all types of pasteurizing plants and presents in detail the equipment and operation of the modern HTST plant (High Temperature Short Time). This section is particularly well illustrated. Part III describes the laboratory control necessary from the producing dairy to the distribution service.

The authors are all English, most of them connected with the National Institute for Research in Dairying, Shinfield, Berkshire, England. Therefore, the terminology employed differs from American usage; however, there is no difficulty or confusion. This text should be available to all technical personnel connected with the pasteurization and processing of community milk supplies.

L. A. F.

The Surgery of Infancy and Childhood: Its Principles and Techniques. By ROBERT E. GROSS, M.D., D.Sc., William E. Ladd Professor of Children's Surgery, The Harvard Medical School. 1000 pages; 18 × 25.5 cm. W. B. Saunders Co., Philadelphia. 1953. Price, $16.00.

Many surgeons have long awaited the publication of this book. Surgeons have repeatedly asked the publisher when another edition of the original Ladd and Gross would be available. Finally, this thousand-page volume is at hand, rewritten by Dr. Gross.

Undoubtedly, it is one of the best books of its type that can be had. It consists of a very complete presentation of general surgical disorders in infants and children. Ample discussion of intrathoracic (pulmonary, esophageal and cardiac) lesions as well as urological problems is included. The uncommon, the rare, as well as the common lesions encountered are all thoroughly recorded. Statistical analyses are enviable. The excellent and numerous illustrations further clarify the well written text.

For any surgeon regularly or occasionally performing surgery upon infants and children, this volume is considered indispensable.

H. H.

Tumors of the Central Nervous System (Atlas of Tumor Pathology, Section X, Fascicles 35 and 37). By JAMES W. KERNOHAN, M.D., and GEORGE P. SAYRE, M.D. 129 pages; 20 × 26 cm. (paper-bound). Published by the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council, Washington, D. C. 1952. Price, 90 cents.

This volume is an addition to the numerous already published fascicles which are a part of an atlas of tumor pathology prepared by the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council. The authors, both seasoned experts, have compiled an excellent set of gross and microscopic illustrations and have balanced these illustrations with cogent authoritative comments, thus placing before the reader a concise, inclusive, authoritative commentary on the *pathology* of tumors of the central nervous system. While some might consider the omission of adrenal, sympathetic, and peripheral neoplasms as an omission of neural tumors, it is to be remembered that the fascicle deals only with tumors of the central nervous system, and

not of all neurogenic tumors. The omission of several rare or controversial forms is not to be criticized. The classifications presented are essentially those of the authors and do not take into consideration the opinion of others. This is not important, as the volume is not primarily intended for student use. In general, the reference is excellent for a quick, thorough appraisal of the more important central nervous system tumors from a strictly pathologic viewpoint. It is not intended to compete with excellent texts which have been written on a clinico-pathological correlative basis. It should be of value, however, to those internists and neurologists whose interests extend into the field of pathology.

J. A. W.

Diseases of Children. 5th Ed., in two volumes. Previous editions edited by Sir A. E. Garrod, K.C.M.G., D.M., F.R.S., Frederick E. Batten, M.D., M.A., F.R.C.P., Hugh Thursfield, D.M., M.A., F.R.C.P., and Donald Paterson, M.D., F.R.C.P. Fifth Edition edited by Alan Moncrieff, C.B.E., M.D., F.R.C.P., Nuffield Professor of Child Health, University of London; and Philip Evans, M.D., M.Sc., F.R.C.P., Physician to the Children's Department and Director of the Department of Child Health, Guy's Hospital; with contributions by 50 authors. 1973 pages (total of both volumes); 15 × 23.5 cm. The Williams & Wilkins Co., Baltimore, Md. 1953. Price, $21.00.

This two volume British work covers pediatrics in a thorough and detailed manner. There are 50 contributors. The style is free as witnessed by the remarks regarding the occasional infant who "like the governor of South Carolina finds the interval between drinks is too long." Some bits of rather quaint lore survive in the books. Thus, question could probably be raised regarding worms and constipation as exciting causes of asthma, "liniment of turpentine and belladonna rubbed into the skin" for bronchitis and regarding the pulmonary antispasmodic effects of tincture of benzoin, oil of eucalyptus or creosote. Some British terms, in particular the names of certain drugs and instruments, are unfamiliar to most American readers.

As in previous editions, the section on growth and development is outstanding. The section on breast feeding is also particularly good, probably reflecting the greater interest and success in breast feeding in that country. The section deploring routine circumcision merits particular attention. Practical pediatric procedures, such as intravenous technics, marrow puncture, spinal puncture, urine collection, etc., are described in detail and well-illustrated. The excessive use of cut-downs for intravenous infusion in infants is discouraged.

The major value of the treatise is in the main lines of thinking, which seem to be sound and timely. The points in which they differ from comparable works in this country represent a valuable broadening of the pediatric textbook literature.

G. E. G.

BOOKS RECEIVED

Books received during September are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Antibiotics. 2nd Ed. By Robertson Pratt, Ph.D., Professor of Pharmacognosy and Plant Physiology, University of California College of Pharmacy, etc.; and Jean Dufrenoy, D.Sci. (Paris), Research Associate in Antibiotics, University of California College of Pharmacy. 398 pages; 24 × 16 cm. 1953. J. B. Lippincott Company, Philadelphia. Price, $7.50.

Bakteriologische Nährböden: Ausgewählte Nährbodenrezepturen für das Medizinisch-Bakteriologische Laboratorium. By Dr. Lothar Hallmann. 252 pages; 21.5 × 15 cm. 1953. Georg Thieme, Stuttgart. Price: Flexibles abwaschbares Ganzleinen DM 19.80.

The Ballistocardiogram: A Dynamic Record of the Heart Beat. Publication Number 143, American Lecture Series. By John R. Braunstein, M.D., Ph.D., Associate Professor of Biophysics and Assistant Professor of Medicine, University of Cincinnati, Cincinnati, Ohio. 84 pages; 22.5 × 14.5 cm. (leather-bound). 1953. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $3.00.

Cancer (Experimental and Clinical). Section XVI of Excerpta Medica. Editors: R. Van Dam and W. Van Westering. 700 to 800 pages a year (published monthly); 24.5 × 17.5 cm. (paper-bound). 1953. Excerpta Medica, N. V., Amsterdam. Price: Subscription rate for Volume I, which will consist of six monthly issues from July to December, 1953, is $5.00 (or the equivalent in local currency). Volume II (1954) and succeeding volumes, which will consist of 12 monthly issues, will be priced at $10.00 a year.

Cardiovascular-Renal Disease in Diabetes Mellitus: A Clinical Study. (Also published as a supplement, No. 281, to Acta Medica Scandinavica, Vol. 146.) By Sverre Aarseth. 252 pages; 24.5 × 17 cm. (paper-bound). 1953. Printed by Bøhler & Larsen, Oslo.

Current Research on Vitamins in Trophology: Proceedings of the Scientific Sessions of the Eighth Annual Meeting, The National Vitamin Foundation, Incorporated, New York City, March 4, 1953. Nutrition Symposium Series Number 7. By W. F. Alexander, S. Corbo, W. J. Darby, Mei Yu Dju, G. Frontali, R. Funaro, M. A. Guzmán, M. K. Horwitt, N. Jolliffe, B. M. Kagan, G. Lanciano, E. W. McHenry, G. Maggioni, K. E. Mason, N. S. Scrimshaw, W. T. Tompkins and Dorothy G. Wiehl. 157 pages; 23 × 15.5 cm. (paper-bound). 1953. The National Vitamin Foundation, Inc., New York. Price, $1.50.

Elementos de Medicina Infantil: Apuntes de la Catedra de Clinica Pediatrica de la Facultad de Ciencias Medicas de la Universidad de San Carlos de Guatemala. By Dr. Carlos M. Monson Malice. Pages not numbered; 24.5 × 16 cm. 1951. Editorial Universitaria, Guatemala.

Enzymatic Concept of Anaphylaxis and Allergy and the Role of Eosinophils in Anaphylactic Reactions Related to Hormonal Alterations. By Z. Z. Godlowski, M.D. (Cracow), Ph.D. (Edin.), M.R.C.P. (Edin.), Research Fellow of the Carnegie Trust, Edinburgh, etc.; Foreword by A. Murray Drennan, M.D., F.R.C.P.E., F.R.S.E., Professor of Pathology, University of Edinburgh. 120 pages; 22.5 × 14.5 cm. 1953. E. & S. Livingstone, Ltd., Edinburgh and London; available in U.S.A. from The Williams & Wilkins Company, Baltimore. Price, $3.50.

Zur Genese des Diabetes mellitus und des Bronchialasthmas. By Prof. Dr. M. Bauer. 113 pages; 23.5 × 15.5 cm. (paper-bound). 1953. Georg Thieme Verlag, Stuttgart. Price, Kartoniert DM 9.60.

The Heart Beat: Graphic Methods in the Study of the Cardiac Patient. By Aldo A. Luisada, M.D., Associate Professor of Medicine and Director, Division of Cardiology, The Chicago Medical School, under a Teaching Grant of the Na-

tional Heart Institute, U. S. Public Health Service, etc. 527 pages; 26 × 18 cm. 1953. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $12.00.

Hormonal Factors in Carbohydrate Metabolism. Volume VI, Ciba Foundation Colloquia on Endocrinology. General Editor for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch.; assisted by JESSIE S. FREEMAN, M.B., B.S., D.P.H. 350 pages; 21 × 14 cm. 1953. Little, Brown and Company, Boston. Price, $6.75.

Insecticides: Manual of Specifications for Insecticides and for Spraying and Dusting Apparatus. Pages not numbered; 26.5 × 18 cm. (loose-leaf binding, hard cover). 1953. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, $8.50.

Die Kreuzschmerzen der Frau. By PROF. DR. HEINRICH MARTIUS. 166 pages; 24 × 16 cm. 1953. Georg Thieme Verlag, Stuttgart; agents for U. S. A.: Grune & Stratton, Inc., New York. Price, Ganzleinen DM 19.50.

Leistungssteigerung: Leistung, Übermüdung, Gesunderhaltung. By PROF. DR. MAX HOCHREIN and DOZ. DR. IRENE HOCHREIN-SCHLEICHER. 283 pages; 24.5 × 17.5 cm. 1953. Georg Thieme Verlag, Stuttgart; agents for U. S. A.: Grune & Stratton, Inc., New York. Price, Ganzleinen DM 27.–

Living with a Disability. By HOWARD A. RUSK, M.D., and EUGENE J. TAYLOR, in collaboration with MURIEL ZIMMERMAN, O.T.R., and JULIA JUDSON, M.S., The Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center. 207 pages; 22 × 14 cm. 1953. The Blakiston Company, Inc., Garden City, New York. Price, $3.50.

Managing Your Coronary. By DR. WILLIAM A. BRAMS; illustrations by HERTHA FURTH. 158 pages; 21 × 14 cm. 1953. J. B. Lippincott Company, Philadelphia. Price, $2.95.

Manual of Medical Emergencies. 2nd Ed. By STUART C. CULLEN, M.D., Professor of Surgery, Chairman, Division of Anesthesiology, State University of Iowa College of Medicine; and E. G. GROSS, M.D., Professor and Head of Department of Pharmacology, State University of Iowa College of Medicine. 278 pages; 18 × 12 cm. 1953. The Year Book Publishers, Inc., Chicago. Price, $4.50.

The National Vitamin Foundation, Incorporated: Annual Report of the Scientific Director, with Introductory Remarks by W. H. Sebrell, Jr., M.D., Director, National Institutes of Health, United States Public Health Service, on New Opportunities in Nutrition Research. 76 pages; 23 × 15.5 cm. (paper-bound). 1953. The National Vitamin Foundation, Incorporated, New York. Volume distributed free of charge each year.

Renal Function: Transactions of the Fourth Conference, October 22, 23, and 24, 1952, New York, N. Y. Edited by STANLEY E. BRADLEY, M.D., Associate Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y. 189 pages; 23.5 × 15.5 cm. 1953. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $3.50.

The Rockefeller Foundation: Annual Report, 1952. 465 pages; 22 × 15 cm. (paper-bound). 1953. The Rockefeller Foundation, New York. Available on request while supply lasts.

Roentgen-Diagnostics. Volume III: Thorax. First American Edition (Based on the Fifth German Edition). By H. R. SCHINZ, W. E. BAENSCH, E. FRIEDL and E. UEHLINGER; English translation arranged and edited by JAMES T. CASE, M.D., D.M.R.E. (Camb.), Professor of Radiology Emeritus, Northwestern University Medical School, Chicago. 1,131 pages; 28 × 19.5 cm. (boxed). 1953. Grune & Stratton, New York. Price, $45.00.

Sexual Behavior in the Human Female. By ALFRED C. KINSEY, WARDELL B. POMEROY, CLYDE E. MARTIN, PAUL H. GEBHARD, Research Associates; and others on the Staff of The Institute for Sex Research, Indiana University. Foreword by ROBERT M. YERKES and GEORGE W. CORNER. 842 pages; 24 × 16 cm. 1953. W. B. Saunders Company, Philadelphia. Price, $8.00.

Symposium on Coal Miners' Pneumoconiosis, Held Under the Auspices of the Golden Clinic, Memorial General Hospital, Elkins, West Virginia, 1952. 95 pages; 21.5 × 14 cm. (paper-bound). 1952. Cornelius Printing Company, Silver Spring, Maryland. Price, $3.50.

A Text-book of Pathology: An Introduction to Medicine. 6th Ed. By WILLIAM BOYD, M.D., Dipl. Psych., M.R.C.P. (Edin.), F.R.C.P. (Lond.), F.R.C.S. (C), LL.D. (Sask.), D.Sc. (Man.), M.D. (Oslo), F.R.S. (C). 1,024 pages; 24 × 15.5 cm. 1953. Lea & Febiger, Philadelphia. Price, $12.50.

Water, Electrolyte and Acid-Base Balance: Normal and Pathologic Physiology as a Basis for Therapy. By HARRY F. WEISBERG, M.D., Assistant Professor of Clinical Pathology and of Clinical Medicine, The Chicago Medical School, etc. 245 pages; 23.5 × 15.5 cm. 1953. The Williams & Wilkins Company, Baltimore. Price, $5.00.

The Year Book of Medicine (1953–1954 Year Book Series). Edited by PAUL B. BEESON, M.D., CARL MUSCHENHEIM, M.D., WILLIAM B. CASTLE, M.D., TINSLEY R. HARRISON, M.D., GEORGE B. EUSTERMAN, M.D., and ROBERT H. WILLIAMS, M.D. 736 pages; 20 × 13.5 cm. 1953. The Year Book Publishers, Incorporated, Chicago. Price, $6.00.

Die Zuckerkrankheit. By PROF. DR. FERDINAND BERTRAM. 175 pages; 24.5 × 17.5 cm. 1953. Georg Thieme Verlag, Stuttgart; agents for U. S. A.: Grune & Stratton, Inc., New York. Price, Ganzleinen DM 19.80.

COLLEGE NEWS NOTES

New Life Member

Dr. Leonard A. Stine, F.A.C.P., Glencoe, Ill., has become a Life Member of the American College of Physicians.

Coming A.C.P. Regional Meetings

A large number of Regional Meetings have been held during October and early November in various parts of the country, with universally gratifying attendance. Customarily programs are sent only to the members in the specific territory covered by a Regional Meeting, but programs for any of these meetings may be obtained by others on request to the Executive Secretary of the College, 4200 Pine St., Philadelphia 4, Pa.

1953

PUERTO RICO—San Juan, November 20 and 21
MIDWEST—Milwaukee, Wis., November 21
NORTH CAROLINA—Chapel Hill, December 3
MICHIGAN—Ann Arbor, December 5

1954

EASTERN PENNSYLVANIA—Philadelphia, January 15
MARYLAND & DISTRICT OF COLUMBIA—Baltimore, January 16
COLORADO—Colorado Springs, January 22–23
SOUTHERN CALIFORNIA—Riverside, February 13 and 14
VIRGINIA—Richmond, February 25
KANSAS—Topeka, March 19
SOUTHERN ILLINOIS—Peoria, March—
NORTH DAKOTA—Bismarck, September 11
NEW ENGLAND—Hartford, Conn., October 22

A.C.P. Postgraduate Courses

Postgraduate Courses sponsored by the American College of Physicians during the autumn of 1953, are now essentially concluded. The last two are Course No. 6, SEMINARS IN INTERNAL MEDICINE, Vanderbilt University School of Medicine, Nashville, Tenn., directed by Drs. Rudolph Kampmeier, F.A.C.P., and Hugh J. Morgan, F.A.C.P., and Course No. 7, THE NEWER BIOLOGICAL AND PHYSIOLOGICAL APPROACHES TO CLINICAL PROBLEMS, University of Wisconsin Medical School, Madison, Wis., directed by Drs. William S. Middleton, M.A.C.P., and Karver L. Puestow, F.A.C.P., both courses being given from November 16 to 20. Course No. 8, BALLISTOCARDIOGRAPHY, Johns Hopkins Hospital, Baltimore, under the direction of Dr. Benjamin M. Baker, Jr., F.A.C.P., will not be given until January 11–13, 1954, but this course was over-subscribed in the early weeks of its announcement. The Committee on Postgraduate Courses is arranging further courses in these specialized and limited fields, according to the success and value of the experimental courses that have been given.

The Committee on Postgraduate Courses met at the College Headquarters on November 14, 1953, and will announce in the next issue of this Journal the proposed

schedule for the spring of 1954. It is anticipated that the following courses will be among those announced:

CLINICAL GASTRO-ENTEROLOGY at New Orleans under Dr. Gordon McHardy.
ALLERGY at Pittsburgh under Dr. Leo H. Criep.
ELECTROCARDIOGRAPHY at Detroit under Dr. Gordon Myers.
HEMATOLOGY at Chicago under Drs. Howard L. Alt, Leon O. Jacobson and L. R. Limarzi.
INTERNAL MEDICINE at New York under Dr. Franklin M. Hanger.
INTERNAL MEDICINE at Philadelphia under Dr. Thomas M. Durant.
NEOPLASTIC DISEASES AND RADIOISOTOPES at New York under Drs. Cornelius P. Rhoads and Rulon Rawson.

A.C.P. Group Malpractice Insurance Plan Improved and Extended

When this Plan was initiated January 1, 1953, the College Brokers, The Association Service Office, 1500 Walnut St., Philadelphia 2, Pa., were sure that our group was definitely in a preferred position. During the first ten months that the Plan has been in force, none of our members who secured protection under this Plan have had claims placed against them, and there are no probable claims of which the brokers have been advised.

Before the initiation of the Plan a study of rates throughout the United States was made, and Lloyds of London agreed to furnish protection for our members at an initial rate of 10% less than the filed rates of the Conference Domestic Companies. As the Plan developed, it became evident that, in a few sections, there were local group Plans that provided rates slightly less than those in our Plan. Members were requested through the Annals to advise our brokers if malpractice protection might be available elsewhere at a lower rate. Thanks to the members who coöperated, essential information was obtained, tabulated and presented to Lloyds' Underwriters. As a result, our brokers have been successful in re-negotiating our Plan, enabling them now to inform the members that many advantages have been added. New rates will shortly be announced, and it is felt that they are lower than any rates that may be secured through a reliable insurance company in America. The rates will include, automatically, coverage for one employee, such as a technician, employed doctor or other assistant. X-ray and radium charges have been reduced and there will be definite stipulated rates for this coverage. Also, provision will be made for electro-shock therapy coverage, for which rates will also be furnished.

The limits of protection have been increased so that the Plan will provide $100/300,000.00 protection. The basic amount of our coverage up to $50/150,000.00 will be under our group contract. Any amount in excess of these limits will be issued as excess coverage, and the member desiring these higher limits will be supplied a special questionnaire to be completed and it will be granted upon special approval from the Underwriters.

The College Brokers have been able to negotiate a definite basis of premium credits, which will become effective as soon as 50% of our eligible members participate in the Malpractice Plan. This should be an incentive for a larger proportion of the members to participate, making it increasingly beneficial to all. The credit formula calls for a reduction of 5% per year for three years, making a total reduction of 15% in premiums. These credits will be available after 50% of our members subscribe, if the loss ratio is satisfactory—anything less than 40% of the premiums collected.

Members are encouraged to renew their Malpractice Insurance coverage under our Group Plan as their individual policies expire. It is only by concerted action

of this character that the College can be of maximum benefit to you in your insurance problems. When you receive the new information from The Association Service Office, read it carefully and send in your application with the effective date desired, which coincides with the termination date of your present insurance. Our brokers hope that a year from now they may be able to announce the first premium credit has been made available due to 50% member subscription and a favorable loss ratio.

Gift to the College Library

Dr. Luis Manuel Morales, F.A.C.P., Clinical Professor of Psychiatry, University of Puerto Rico School of Medicine, San Juan, has presented a *"Primer on Psychiatry, Neurology and Mental Hygiene"* to the Library of the College. It was written at the request of and published by the Department of Education of the Commonwealth of Puerto Rico, and is the first of a series of monographs by various medical specialists for the education of the general public in matters of health and hygiene.

Postdoctoral Fellowships Available

The National Foundation for Infantile Paralysis announces the availability of a limited number of additional postdoctoral fellowships to candidates whose interests are research and teaching in medicine and the related biological and physical sciences. The purpose of these National Foundation fellowships is to increase the number of professional workers qualified to give leadership in the solution of basic and clinical research problems, including those of poliomyelitis and other crippling diseases.

The fellowships cover a period of from one to five years. Stipends to Fellows range from $3,600–$7,000 a year, with marital and dependency status considered in determining individual awards. Institutions which accept Fellows receive additional compensation for expenses incurred in relation to their training programs.

Eligibility requirements include United States citizenship (or the declared intention of becoming a citizen), sound health and an M.D., Ph.D., or an equivalent degree. Selection of candidates is made by a Fellowship Committee composed of leaders in the fields of medical research and professional education. The designation "Fellow of The National Foundation for Infantile Paralysis" will be given to successful candidates.

Complete information concerning qualifications and applications may be obtained from: Division of Professional Education, The National Foundation for Infantile Paralysis, 120 Broadway, New York 5, New York.

Award for Outstanding Research in the Field of Infertility

The American Society for the Study of Sterility announces the opening of the 1954 contest for the most outstanding contribution to the subject of infertility and sterility. The winner will receive a cash award of $1,000.00 and the essay will appear on the program of the 1954 meeting of the Society. Essays submitted in this competition must be received not later than March 1, 1954. For full particulars concerning requirements of this competition, address The American Society for the Study of Sterility, c/o Dr. Herbert H. Thomas, Secretary, 920 S. 19th St., Birmingham 5, Ala.

The author should append on a separate sheet of paper a short biographical sketch of himself and include a photograph to be used in the necessary publicity should he be the winner of the award.

Systemic Mycoses Course

Southwestern Medical School of the University of Texas announces a course in Systemic Mycoses to be presented in Dallas, Jan. 18–20, 1954. Particulars concerning the course may be obtained from the Office of the Dean, 2211 Oak Lawn Ave., Dallas 19, Tex.

Dr. Charles F. McKhann, F.A.C.P., Professor of Pediatrics, Jefferson Medical College of Philadelphia, is Chairman of the Clinical Advisory Board of United Cerebral Palsy. The advisory boards give professional guidance to United Cerebral Palsy in planning and carrying out its national programs of research, education of palsied children, and vocational guidance and placement of cerebral palsy adults.

Dr. Carl J. Wiggers, F.A.C.P., who recently retired as Director of the Department of Physiology, Western Reserve University School of Medicine, Cleveland, is now associated with the Frank E. Bunts Educational Institute, Cleveland Clinic Foundation. On the anniversary of his 70th birthday, May 28th, Dr. Wiggers was the recipient of the honorary degree, Doctor of Medicine honoris causa, from the Medical Faculty of the Ludwig-Maximilian University of Munich, Germany. Dr. Wiggers was a pupil of Otto Frank in the Physiological Institute of that University in 1912.

Dr. Marion A. Blankenhorn, F.A.C.P., Professor of Medicine at the University of Cincinnati College of Medicine, recently served as Professor of Medicine Pro Tem at Georgetown University School of Medicine, Washington, D. C., and acted in an advisory capacity on educational activities to the Department of Medicine at Georgetown University Hospital and to the medical school.

Dr. Charles S. Holbrook, F.A.C.P., retired on July 1 as Professor of Clinical Psychiatry at Tulane University of Louisiana School of Medicine, New Orleans.

Dr. Walter L. Bierring, F.A.C.P., now 84 years of age, has retired as Health Commissioner for the State of Iowa. At a testimonial dinner in his honor at the Des Moines Club, a certificate of appreciation was presented to Dr. Bierring for his long period of service to the state and to the medical profession. Dr. Bierring was formerly President of the American Medical Association (1934) and of the Iowa State Medical Society and of the Johnson and Polk Counties Medical Societies. He has been President of Alpha Omega Alpha for some twenty years. He was formerly a Regent and Vice President of the American College of Physicians and was the first Chairman of the American Board of Internal Medicine.

Dr. Max Caplan, F.A.C.P., has been advanced to Assistant Clinical Professor of Medicine at Yale University School of Medicine.

Dr. C. W. Holland, F.A.C.P., College Governor for the Maritime Provinces, was the Official Representative of the American College of Physicians recently at the Centenary of Saint Francis Xavier at Antigonish, Canada.

Rear Admiral Arthur H. Dearing, (MC), USN (Ret'd), assumed his duties Oct. 1 as Executive Secretary of the College of American Pathologists. He is a former member of the Board of Governors of the Armed Forces Institute of Pathology

and is at present serving on the Board of Governors of the American College of Surgeons. He completed 35 years of Naval service. He is a native of Maine, a resident of San Francisco, and a graduate of Dartmouth College and Harvard Medical School.

Trudeau Sanatorium, Trudeau, N. Y., a private, non-profit institution for the diagnosis and treatment of diseases of the chest, particularly pulmonary tuberculosis, has recently issued a pamphlet entitled "Answers to Questions from Physicians about Trudeau Sanatorium," the purpose of which is to give physicians the latest information about Trudeau. Trudeau Sanatorium was established 70 years ago by Dr. Edward Livingston Trudeau, a pioneer in the research and clinical aspects of tuberculosis. It has grown from one cottage accommodating two patients to a village of 52 buildings with a capacity of 175 patients. On its staff are five Diplomates of American Boards, including three of Internal Medicine and one each of Preventive Medicine and Radiology. Its research facilities include the departments of bacteriology, biochemistry, pathology, physiology and roentgenology. It is located in the Adirondack Mountains in Northern New York at an elevation of 1,650 feet, overlooking the mountains and the Saranac River Valley. Its purpose is to provide, at moderate cost, proper treatment of tuberculosis for those who prefer to be cared for in a private sanatorium rather than at home or in a public institution. Dr. Roger S. Mitchell, F.A.C.P., is the Associate Medical Director.

Dr. David Cayer, F.A.C.P., has been promoted to Professor of Gastroenterology at the Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.

Dr. Alvin G. Foord, F.A.C.P., has resigned as Director of Laboratories at the Collis P. and Howard Huntington Memorial Hospital, Pasadena, Calif., after 22 years of service. He will now serve as Consulting Pathologist.

Dr. Jerome S. Levy, F.A.C.P., Little Rock, is President of the Arkansas Tuberculosis Association.

Dr. H. Milton Rogers, F.A.C.P., St. Petersburg, was recently installed as President of the Florida Heart Association, and Dr. Alvin E. Murphy, F.A.C.P., Palm Beach, was made President-Elect.

Dr. J. S. L. Browne, F.A.C.P., Montreal, addressed the dinner meeting of the New York Diabetes Association, Oct. 8, on "Certain Concepts and Difficulties in Clinical Endocrinology."

Dr. E. Osborne Coates, Jr. (Associate), Trudeau, N. Y., has recently been appointed Chief of the Chest Service at the Henry Ford Hospital in Detroit. He will assume his new duties on Feb. 1, 1954, and is resigning as Assistant Medical Director of the Trudeau Sanatorium as of Jan. 1.

Under the Presidency of Dr. Charles E. Watts, F.A.C.P., Seattle, the Washington State Medical Association held its yearly meeting in Seattle, Sept. 13–16. Dr. Chester M. Jones, F.A.C.P., Boston, discussed "Trigger Mechanisms and Digestive Tract Symptoms." Drs. Lester J. Palmer, F.A.C.P., and Robert H. Williams, F.A.C.P., Seattle, were among the participants in a panel discussion on "Clinical Endocrinology." Dr. Williams also acted as moderator for the symposium on endocrinology.

Dr. Kenneth E. Appel, F.A.C.P., Philadelphia, and Dr. Daniel Blain, F.A.C.P., Washington, D. C., were among the guest speakers at the meeting of the Mid-Continent Psychiatric Association, which convened in Kansas City, Mo., Sept. 26–27.

Dr. Charles A. Poindexter, F.A.C.P., New York, spoke on "Heart Disease in Pregnancy" at an Obstetric Seminar in Daytona Beach, Fla., Sept. 14–16. The Seminar was sponsored by the Maternal Welfare Committee of the Florida Medical Association and the Bureaus of Maternal and Child Health of South Carolina, Georgia and Florida.

Dr. Garfield G. Duncan, F.A.C.P., Clinical Professor of Medicine at Jefferson Medical College of Philadelphia, in August headed a three-week course in Internal Medicine under the auspices of the New Zealand Postgraduate Association in Auckland and delivered the Cunning Memorial Lecture on "Undernutrition as Encountered in General Practice" before the Royal Australasian College of Physicians at Dunedin, and also lectured in Sydney, Australia, on "Essential Hypertension."

The Kanawha Medical Society presented a one-day course in "Modern Advances in Cardiac Therapy" at Charleston, W. Va., on Sept. 16, the faculty being composed of Dr. Ralph E. Dolkart, F.A.C.P., Northwestern University Medical School, Chicago; Dr. R. W. Kissane, F.A.C.P., Ohio State University College of Medicine, Columbus; Dr. Edward S. Orgain, Sr., F.A.C.P., Duke University School of Medicine, Durham; Dr. Charles P. Bailey, Hahnemann Medical College of Philadelphia, and Dr. Francis F. Rosenbaum, F.A.C.P., Marquette University School of Medicine, Milwaukee. About 150 physicians were in attendance.

Dr. Leonard Cardon, F.A.C.P., Chicago, was a guest speaker at the semi-annual meeting of the 11th Councilor Medical District of Indiana, at Huntington, Sept 16. His subject was "Acute Medical Emergencies—Some Practical Considerations in the Diagnosis and Management of Acute Coronary Occlusion."

Major Gen. Harry G. Armstrong, F.A.C.P., The Surgeon General of The U. S. Air Force, was the recipient recently of the highest award of the French Air Force Medical Service, a gold Medal of Honor. Brig. Gen. Otis O. Benson, Jr., F.A.C.P., at the same time received the award of a Medal of Honor of the second class. The awards were made in recognition of assistance rendered by these officers to aviation medicine in France. It is said to mark the first occasion on which a top decoration for aviation medicine in France has been given to an officer of another nation.

Dr. O. Jocevious Farness, F.A.C.P., Tucson, has been appointed, by Governor Howard Pyle, a member of the Arizona State Board of Medical Examiners for a term of three years.

Dr. Richard M. Burke, F.A.C.P., Oklahoma City, is President of the new Oklahoma Trudeau Society. The National Tuberculosis Association announces that there are now 28 sections or state Trudeau Societies.

Dr. Frank J. Holroyd, F.A.C.P., Princeton, has succeeded Dr. Walter E. Vest, F.A.C.P., Huntington, as President of the West Virginia Medical Licensing Board.

At the annual meeting of the American Dietetic Association, which convened in Los Angeles, Aug. 25–28, Dr. Laurance W. Kinsell, F.A.C.P., Oakland, gave a talk on "Comparative Effects of Diets Containing Large Amounts of Animal and Vegetable Fat Respectively, upon Serum Lipids in Normal and Abnormal Human Subjects" as part of the program of "Newer Findings in Diet Therapy." At the same meeting, Dr. Garnett Cheney, F.A.C.P., San Francisco, discussed "The Present Status of Vitamin U Therapy in the Dietary Treatment of Peptic Ulcer" in the section on "Recent Research." Dr. James A. Halsted, F.A.C.P., Los Angeles, was one of the panel members in a discussion on "Coöperative Approach Aids Medical Therapy." Other members of the College who participated in the program included Dr. Samuel Soskin, F.A.C.P., Los Angeles, who read a paper entitled "Newer Concepts in the Treatment of the Diabetic," and Dr. Harold I. Harvey (Associate), Berkeley, who discussed "The Obesity Problem."

Dr. Joseph Lee Hollander, F.A.C.P., Philadelphia, used as his topic "Cortisone and Hydrocortisone in Surgery" in addressing the meeting of the International College of Surgeons, held in New York City, Sept. 13–17.

Among the guest speakers at the 21st Annual Assembly of the Omaha Mid-West Clinical Society, held Oct. 26–29, were Dr. Grace A. Goldsmith, F.A.C.P., New Orleans, Dr. Francis J. Braceland, F.A.C.P., Hartford, Conn., Dr. William S. Hoffman, F.A.C.P., Chicago, and Dr. Lewis M. Hurxthal, F.A.C.P., Boston.

Dr. Robert L. King, F.A.C.P., Seattle, Wash., President of the American Heart Association, was one of the luncheon speakers during an Industrial Health Conference, held Oct. 1–3 in Houston, Tex. Dr. Sidney Schnur, F.A.C.P., Houston, presided at a panel meeting which included "A Problem for the Insurance Carrier" by Dr. E. Ghent Graves, Sr. (Associate), Houston. The Conference was sponsored by the Texas Heart Association and the Houston District Chapter in coöperation with other groups.

Dr. Edgar Mayer, F.A.C.P., New York, spoke on "Palliative Treatment of Inoperable Bronchogenic Carcinoma" at the dinner held during the annual meeting of the Wisconsin Chapter of the American College of Chest Physicians, which met in Milwaukee, Oct. 4. Dr. George A. Hellmuth, F.A.C.P., Chicago, discussed "Electrocardiographic Problems in Daily Practice," and Dr. Joseph M. Lubitz, F.A.C.P., Milwaukee, gave a presentation entitled "Granulomatous Lung Disease."

Dr. Leon O. Jacobson, F.A.C.P., Chicago, discussed "Objectives in Medical Use of Radioisotopes and High Energy Radiation" at the annual meeting of the American Chemical Society in Chicago during the week of Sept. 6.

Dr. Elliott P. Joslin, M.A.C.P., and Dr. Hermann L. Blumgart, F.A.C.P., Boston, discussed, respectively, "Clinical Application of Statistical Studies in Diabetes" and "Angina Pectoris and Its Treatment" as their contributions to the fall series of lectures sponsored by the Hartford (Conn.) Medical Society. Dr. Joslin also delivered the Sixth Annual Harvard Lecture on "Diabetes Today and Tomorrow" at the University of Colorado Medical Center, Denver, Oct. 30.

Dr. Benjamin M. Gasul, F.A.C.P., Chicago, gave a series of three lectures on "Recent Advances in Pediatric Cardiology" at the City of Hope, Duarte, Calif., and the Cedars of Lebanon Hospital, Los Angeles, in early September.

Col. Carl W. Tempel, (MC), USA, F.A.C.P., Denver, recently gave the annual Hyman I. Spector Lecture at the St. Louis University School of Medicine.

The National Gastroenterological Association held its 18th Annual Convention and Course in Postgraduate Gastroenterology at the Biltmore Hotel, Los Angeles, Oct. 12–17. The following members of the College were among the speakers and officers of instruction: Dr. Julius Bauer, F.A.C.P., Dr. William C. Boeck, F.A.C.P., Dr. John S. Lawrence, F.A.C.P., Dr. Lester M. Morrison, F.A.C.P., Dr. David Niemetz, F.A.C.P., Dr. Rudolf Schindler, F.A.C.P., Dr. Paul Starr, F.A.C.P., Dr. George K. Wharton, F.A.C.P., Dr. Olov A. Blomquist (Associate), Dr. Robert R. Commons (Associate), Dr. James A. Halsted, F.A.C.P., Dr. Jacob Lichstein (Associate), Dr. William E. Molle (Associate), all of Los Angeles; Dr. Garnett Cheney, F.A.C.P., San Francisco; Dr. Anthony Bassler, F.A.C.P., New York; Dr. Joseph Shaiken, F.A.C.P., Milwaukee, Wis.; Dr. Joseph Bank, F.A.C.P., and Dr. Marcy L. Sussman (Associate), Phoenix, Ariz.; Dr. Hyman I. Goldstein, (Associate), Camden, N. J.; and Dr. Stephen J. Stempien, (Associate), Beverly Hills, Calif. Dr. Sigurd W. Johnsen, F.A.C.P., Passaic, N. J., was installed as President at the banquet on Oct. 13.

At the annual Scientific Assembly of the Connecticut Chapter of the American Academy of General Practice, held in Hartford, Oct. 8, Dr. Joseph B. Vander Veer, F.A.C.P., Philadelphia, presented a paper on "Diagnosis and Treatment of Acute Cardiovascular Emergencies," and Dr. Edward Weiss, F.A.C.P., Philadelphia, spoke on "The Diagnosis and Treatment of Psychosomatic Disorders."

Dr. William C. Kuzell (Associate), San Francisco, spoke before the Eighth International Congress on Rheumatic Diseases, held recently in Geneva, Switzerland. His paper concerned the clinical results obtained from the use of phenylbutazone in the treatment of arthritis and gout.

Dr. George T. Harrell, Jr., F.A.C.P., Professor of Medicine at the Bowman Gray School of Medicine, Winston-Salem, N. C., used "Myxedema" as his topic in addressing the staff of the Bluefield (W. Va.) Sanitarium at its first annual clinical seminar on Oct. 2.

Dr. Samuel P. Asper, Jr. (Associate), Associate Professor of Medicine at Johns Hopkins University School of Medicine, Baltimore, was among the guest speakers at the North Texas-Southern Oklahoma Fall Clinical Conference, held in Wichita Falls, Tex., Sept. 16. His subjects were "Clinical Use of Cortisone and ACTH" and "Newer Aspects in Treatment of Thyroid Diseases."

Dr. Jerome W. Conn, F.A.C.P., Professor of Internal Medicine at the University of Michigan Medical School, Ann Arbor, discussed "Spontaneous Hypoglycemia: Differential Diagnosis and Management" at the annual meeting of the Ohio Academy of General Practice, held in Cleveland, Sept. 16–17.

Dr. Ralph Bowen, F.A.C.P., Houston, Tex., and Dr. Harold E. Stadler, F.A.C.P., Indianapolis, Ind., were among the guest speakers at a Postgraduate Conference in Pediatrics, held Sept. 16–17 in Iowa City. Their respective subjects were "Allergy in Identical Twins" and "Heredofamilial Cerebral Degeneration in Infancy: The Relationship of Systemic Factors to the Pathogenicity." The Conference was conjointly sponsored by the Department of Pediatrics of the State University of Iowa

College of Medicine, the Iowa Pediatric Society, the Maternal and Child Health Division of the State Department of Health and the State University of Iowa Council on Children and Youth.

Dr. Benjamin M. Gasul, F.A.C.P., Chicago, and Dr. Paul Gyorgy, F.A.C.P., Philadelphia, were among the participants in the program of the Seventh International Congress of Pediatrics, held in Havana, Cuba, Oct. 12–17, following the annual meeting of the American Academy of Pediatrics in Miami, Fla.

Under the Presidency of Dr. Clair L. Stealy, F.A.C.P., San Diego, Calif., the annual meeting of the American Association of Medical Clinicians was held in Chicago, Oct. 9–11. Dr. Wayne Gordon, F.A.C.P., Billings, Mont., acted as moderator for a panel on "Prepaid Medical Care Plans: Status and Problem." Dr. Edwin P. Jordan, F.A.C.P., Charlottesville, Va., Executive Director of the Association, discussed "Professional Composition of Group Practices" before the professional problems session. Dr. R. Franklin Jukes, F.A.C.P., Akron, Ohio, moderated a panel discussion of "Problems in Internal Structure and Organization of Clinics."

Dr. Maxwell M. Wintrobe, F.A.C.P., Salt Lake City, speaking on "Anaemia of Infection," was among the speakers at the first meeting of the Western Tuberculosis Conference, held in Salt Lake City, Sept. 17–19. Dr. John W. Berry, F.A.C.P., Denver, was one of three co-authors of the paper on "Place of Slide Culture in Pulmonary Tuberculosis and Suspected Tuberculosis." Dr. John Z. Bowers, F.A.C.P., Salt Lake City, presided over the general session, held following the banquet Friday evening.

Many members of the College contributed to the success of the annual fall meeting of the North Pacific Society of Internal Medicine when the Society convened at Harrison Hot Springs, B.C., Can., Sept. 18–19. Speakers and their topics included the following: Dr. Charles N. Holman, F.A.C.P., Portland, Ore., "The New General Hospital at the University of Oregon Medical School"; Dr. Joseph H. Delaney, Sr., F.A.C.P., Spokane, Wash., "Thyrotoxic Heart Disease"; Dr. Russell B. Hanford, F.A.C.P., Spokane, Wash., "Are Vagal Inhibitors of Use in Treatment of Intermittent Atrioventricular Block?" Dr. Ralph H. Huff, F.A.C.P., Tacoma, Wash., "Clinical Conditions Stimulating Coronary Artery Disease"; Dr. Kyran E. Hynes, F.A.C.P., Seattle, "Significance of Cardiac Vectors"; Dr. Robert H. Williams, F.A.C.P., Seattle, "Recent Advances Relative to Diabetes"; Dr. Earl D. DuBois, F.A.C.P., Portland, "Diagnosis and Treatment of Disturbances Arising from the Sphincter of Oddi"; Dr. George A. Boylston, F.A.C.P., Portland, "Peptic Ulcer of the Pyloric Ring"; Dr. E. Murray Burns (Associate), Portland, "Emulsifying Agents in Digestive Disorders."

Dr. Joseph C. Edwards, F.A.C.P., St. Louis, addressed the 75th anniversary meeting of the Montana Medical Association, held in Billings, Sept. 17–20. His topic was "Diagnosis and Treatment of Essential Hypertension."

Dr. Priscilla White, F.A.C.P., Boston, discussing "Diabetes in Pregnancy," was one of the out-of-state speakers at the 58th Annual Meeting of the Utah State Medical Association and the Seventh Biennial Rocky Mountain Medical Conference, held at the University of Utah, Salt Lake City, Sept. 10–12.

Dr. Irvine H. Page, F.A.C.P., Cleveland, and Dr. Henry A. Schroeder, Sr., F.A.C.P., St. Louis, were among the guest speakers at a cardiovascular symposium sponsored by the Vermont and New Hampshire Heart Associations and the University of Vermont College of Medicine and held in Burlington, Vt., Sept. 8–10. Dr. Schroeder talked on "Control of Hypertension," while Dr. Page discussed "Neural and Hormonal Control of the Blood Vessels" and was guest speaker at the seminar on "Hormones and Nerves in Cardiac Pathology and Therapy," which was conducted by Dr. Wilhelm Raab, F.A.C.P., Professor of Experimental Medicine at the University of Vermont College of Medicine, Burlington. Dr. Charles E. Kossmann, F.A.C.P., New York, and Dr. Harold D. Levine, F.A.C.P., Boston, participated in the seminar on electrocardiography.

Dr. Richard D. Kepner, F.A.C.P., of Honolulu, attended the Annual Meeting of the Royal Medico-Psychological Association in Gloucester, England, in July. On his way back to Honolulu, he addressed the Delhi Medical Association and the Thailand Medical Association on the subject, "Some Aspects of Psychiatry for the General Practitioner."

OBITUARIES

NEWELL C. GILBERT

Newell Clark Gilbert, M.D., F.A.C.P., was born on December 5, 1880, and died on August 1, 1953, in the seventy-third year of his life. Dr. Gilbert was the son of Elizabeth Clark Gilbert and Dean Newell D. Gilbert, Professor of Psychology at Illinois State Teachers College.

Dr. Gilbert received his M.D. degree from Northwestern University Medical School in 1907 and taught continuously at the Medical School until the time of his death. He was Chairman of the Department of Medicine from 1939 until his retirement in August of 1950.

Dr. Gilbert was appointed to the Attending Staff of St. Luke's Hospital in 1916 and served that institution well in many capacities. He was Editor-in-Chief of the *Archives of Internal Medicine* from 1932 to 1950, and one of the founders of the Chicago Heart Association.

In Chicago he worked with many groups and committees, always looking toward the improvement of medicine in Chicago. He was a stimulating teacher and a tireless investigator—especially in the field of cardiovascular disease. He contributed many fine papers on the coronary circulation, a field in which he always had a deep interest. While his main interest was cardiology, he always kept a wide vision in the entire field of internal medicine.

He was a member in many medical organizations, including the Chicago Medical Society, Illinois State Medical Society, Institute of Medicine of Chicago, American Medical Association, Chicago Society of Internal Medicine, American Society for Clinical Investigation, Association of American Physicians, American Heart Association, the Chicago Heart Association and others. Dr. Gilbert was a Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Physicians since 1944.

He was intensely human and always interested in human beings. Behind what looked like a gruff exterior at times, there was always a deep sense of humor. Dr Gilbert will be sorely missed.

He will be succeeded by his younger colleagues, but they cannot replace him. He was the type of scholarly gentleman of whom there are too few in the world today. Besides a host of friends, he is survived by his widow, Charlotte Pettibone Gilbert, to whom he was married in 1914; a son, Dr. Robert P.; a daughter, Mary Elizabeth; and a sister, Julia E. Gilbert.

HOWARD WAKEFIELD, M.D., F.A.C.P.,
Governor for Northern Illinois

DR. IRVING GRAY

Dr. Irving Gray, a Fellow of the American College of Physicians, died on April 21, 1953, from arteriosclerotic heart disease.

He was born in Brooklyn, on July 31, 1892. He received his degree of Doctor of Medicine from New York University and Bellevue Hospital Medical College in 1913. Following this he studied in Berlin, Vienna and Frankfurt. He interned at the Jewish Hospital and later became Assistant Attending Physician, Associate Attending Physician, and Chief of the Gastro-intestinal Clinic. He was Attending Physician and Consulting Gastro-enterologist to the Brooklyn State Hospital, beginning in 1930. He served as Consulting Physician in the Rockaway Beach, Long Beach Memorial, and St. Joseph Hospitals. He was also Attending Physician in the Sea View Hospital, Staten Island, and the Coney Island and Harbor Hospitals. He formerly served as Assistant Gastro-enterologist at Bellevue Hospital Medical

College Clinic, and Gastro-enterologist at the Brooklyn Hebrew Home and Hospital for the Aged.

During World War I, Dr. Gray served as a Lieutenant in the Medical Corps of the U. S. Navy. During World War II, he acted as a Consultant in Medicine to Selective Service Boards and was cited by Congress for his Selective Service work. He held the rank of Surgeon, U.S.P.H.S. (R), but did not see active duty.

In 1937–1938, Dr. Gray served as President of the Second District Branch, New York State Medical Society. He served as an officer of the Association for Advancement of Industrial Medicine and Surgery, the New York State Industrial Medicine Association, and the Brooklyn Industrial Health Committee. He was a Diplomate of the American Board of Internal Medicine, a Fellow of the American College of Physicians since 1926, a Fellow of the American Public Health Association, an honorary member of the American Association of Industrial Physicians and Surgeons. In addition to other societies, he was also a member of the American Heart Association, the National Tuberculosis Association, and Phi Delta Epsilon fraternity.

It is with deep regret that his friends and colleagues note the loss of Dr. Gray at this time.

IRVING S. WRIGHT, M.D., F.A.C.P.,
Governor for Eastern New York

DR. MICHAEL ROBERT HALEY

Dr. Michael Robert Haley, F.A.C.P., of Dayton, Ohio, died on May 28, 1953, of a cerebral hemorrhage. He was born in Wilmington, Ohio, on May 25, 1885. He graduated from the St. Louis University School of Medicine in 1913. He practiced medicine in Piqua, Ohio, for a number of years before moving to Dayton, where he continued his practice.

He formerly attended Wilmington College at Wilmington and St. Xavier University at Cincinnati, Ohio. He interned at Providence Hospital in Washington, D. C., from 1913 to 1915. Dr. Haley served in World War I as a Captain in the Army Medical Corps. He was formerly a member of the medical staff of St. Elizabeth Hospital and later became Chief of Staff of Good Samaritan Hospital, both in Dayton.

He was made an Associate in the American College of Physicians in 1930 and became a Fellow in 1933. He was a Diplomate of the American Board of Internal Medicine, a member of the Montgomery County, Ohio State, and American Medical Associations, and also a member of the Dayton Academy of Medicine.

Dr. Haley was a devoted follower of the Catholic faith all his life, being a member of the Corpus Christi Church of Dayton, a member of the Knights of Columbus, a member of the Dayton University Club, and also a member of the Optimist Club.

It can be truly said of Dr. Haley that he was one of Dayton's most prominent and best beloved physicians. He was widely known for his interest in civic and medical activities. He was not only a physician to his patients but he was also their devoted friend. It has been said by all of his contemporary physicians that he stood for all that was good and fine in medicine.

Dr. Haley was always the perfect gentleman. He was always courteous, kind, and willing to help. He stood for the highest principles at all times. He will be greatly missed by his former patients, and his friends in the medical profession will always look back with the fondest memories "that when Mike was present we were in for a good, sincere, and honest discussion." He was always able and willing to advise us wisely, and all the doctors in Dayton will greatly miss Mike.

A. B. BROWER, M.D., F.A.C.P.

DR. EDWIN P. KOLB

Dr. Edwin Paul Kolb, F.A.C.P., of Patchogue, N. Y., died on June 14, 1953, of a myocardial infarction.

Dr. Kolb was born in Frostburg, Md., July 8, 1883. He received his degree of Doctor of Medicine from the University of Maryland School of Medicine in 1912. For many years he served as Superintendent of the Suffolk Sanatorium, and had formerly acted as Consultant to the South Side, Kings Park State, John T. Mather Memorial, Central Islip State, Pilgrim State, and Southampton Hospitals, and the St. Charles Hospital for Crippled Children. At one time he was Director of Tuberculosis Clinics of the Suffolk County Department of Health. He retired from active professional work in June, 1949, and removed from Holtsville, N. Y., to Patchogue.

Dr. Kolb, who had served as a Major in World War II, was a Diplomate of the American Board of Internal Medicine and had been a Fellow of the American College of Physicians since 1931. He was formerly President of the Associated Physicians of Long Island and the South Side Clinical Society, and a former Secretary of the Suffolk County Medical Society. He was a member of the Medical Society of the State of New York, American Medical Association, American Sanatorium Association, and the Association of Military Surgeons.

It is with deep regret that we record the passing of Dr. Kolb.

IRVING S. WRIGHT, M.D., F.A.C.P.,
Governor for Eastern New York

DR. CHARLES K. MAYTUM

Dr. Charles Koran Maytum, F.A.C.P., died April 10, 1953, at his home in Rochester, Minn., after a long illness, of coronary sclerosis.

Dr. Maytum was born December 20, 1895, at Alexandria, S. D. He attended the University of South Dakota from 1913 to 1915 and received the degree of M.D. in 1919 from the State University of Iowa College of Medicine. He interned at the Cincinnati General Hospital in 1919 and 1920 and was Receiving Physician the following year. He was in practice at Alexandria from 1921 to 1922.

Dr. Maytum entered the Mayo Foundation as a Fellow in Medicine in July, 1922, and was on leave of absence from December 20, 1922, to March 6, 1923. He was appointed to the staff of the Mayo Clinic in 1926 and later became head of a section in the Division of Medicine. In 1927 he became Instructor in Medicine, Mayo Foundation, Graduate School, University of Minnesota; Assistant Professor in 1934, Associate Professor in 1945, and eventually Professor of Medicine. Later he became Senior Consultant, Division of Medicine, Mayo Clinic.

During World War II, Dr. Maytum entered the Medical Corps of the Army of the United States as Lieutenant Colonel and was promoted to Colonel, serving from August, 1943, to January, 1946. He was Chief of Medicine of the 237th Station Hospital in New Guinea, where he was stationed for 19 months. He was awarded the Bronze Star medal and the Asiatic-Pacific theater ribbon.

Dr. Maytum was certified in internal medicine and allergy by the American Board of Internal Medicine in 1937. He had been a Fellow of the American College of Physicians since 1930 and was a member of the Minnesota State Medical Association, the Southern Minnesota Medical Association, the American Medical Association, the American Academy of Allergy, the Alumni Association of the Mayo Foundation, and Phi Rho Sigma and Sigma Xi fraternities.

LOUIS E. PRICKMAN, M.D., F.A.C.P.

DR. BENEDICT OLCH

Dr. Benedict Olch, F.A.C.P., of Dayton, Ohio, died on June 27, 1953, of coronary heart disease. Dr. Olch was born December 16, 1893, in Providence, R. I. He attended the schools there and graduated from Brown University in 1915 and from the Harvard Medical School in 1919.

He interned in New York at the New York City and Harlem Hospitals and in Providence at St. Joseph's Hospital and at the Providence City Hospital. He came to Dayton soon after finishing his internship to begin the practice of medicine. Dr. Olch confined his efforts practically all his life to the practice of internal medicine.

For many years he was on the medical staff at the Miami Valley Hospital, and at one time he was Senior Visiting Physician and Cardiologist at the Good Samaritan Hospital.

Dr. Olch was made an Associate of the American College of Physicians in 1929 and a Fellow in 1932. A Diplomate of the American Board of Internal Medicine, he was a member of the Montgomery County Medical Association, the Ohio State Medical Association and a Fellow of the American Medical Association.

It is interesting to note that aside from the fact that he was an outstanding physician, Dr. Olch was a very accomplished pianist and many times entertained his friends in this manner. He was a most serious student and was always foremost in his research accomplishments. He was devoted to his practice and to his patients. A number of years ago he unfortunately had a series of coronary accidents which necessitated his giving up the practice of medicine in 1941.

However, although he did not indulge or become involved in the practice of medicine, he constantly studied and kept abreast of the most recent literature. When his condition was such that he could participate, he attended medical meetings; frequently his discussions were outstanding.

Dr. Olch was a true friend and could be counted upon in time of need, regardless of what it might cost him personally. His many friends and the community will miss him sorely.

A. B. Brower, M.D., F.A.C.P.

DR. JOHN ELMER PLUNKETT

Dr. John Elmer Plunkett was born in Peterborough, Ontario, on April 17, 1900 and died in Ottawa on January 11, 1953. He was graduated in Pharmacy from the University of Toronto in 1922 and in Medicine from Queen's University, Kingston, in 1930. After two years of internship at the Ottawa Civic Hospital he spent three years as a Fellow in Medicine at the Mayo Foundation. Returning to Ottawa in 1935, he continued to study Medicine as he practised it. He passed the Fellowship examination of the Royal College of Physicians of Canada in 1936. He became a Fellow of the American College of Physicians in 1938 and in the same year was granted the diploma of the American Board of Internal Medicine. He was appointed Assistant Honorary Secretary of the Royal College of Physicians and Surgeons of Canada in 1939 and Honorary Secretary in 1946. He served the Canadian College in that capacity with great distinction till his death. He also served as Assistant Professor of Medicine of Queen's University, teaching their students on the wards of the Ottawa Civic Hospital with interest, skill and understanding; and as Chairman of the Postgraduate Education Committee of his hospital he contributed greatly. He was an eminent consultant, loved by his colleagues and patients and unable to meet the demands on his time.

Dr. Plunkett was also a member and Vice-President of the Ottawa Academy of Medicine, a member of the Ottawa Medical Literary Club, the Ottawa Bacteriological Club, the Ontario Medical Association, the Canadian Medical Association, Canadian Physiological Society, Alumni Society of the Mayo Foundation, Minnesota State Medical Society, American Medical Association and the American Heart Association.

He became one of the best known physicians in Canada. His work in the Royal College during its period of rapid expansion had a remarkable effect in raising the standards of postgraduate training, medical practice and hospital care all across the country. The Fellows, Officers and Staff of the College depended greatly on him. They relied on his wonderful memory for detail, his ability to understand sectional

problems and to write satisfactory answers to difficult questions, and his wise advice and judgment, and they admired him greatly as a man.

He was a quiet, kindly, modest, highly honorable and very conscientious person who worked with great intensity and apparently unexpendable energy in spite of his thin and somewhat frail appearance. His willingness to help everyone was unlimited and he possessed in a wonderful degree the ability to understand and make his help effectual. It was obvious that he enjoyed all his numerous activities in different fields: his Royal College work, his teaching, his hospital work, the numerous other community and social activities with which he was associated, his medical practice, his friendship for his colleagues in all his endeavors, and his love and care of his family. By the breadth and dependability of his character, his magnanimity, his selfless aim for a goal of excellence, he seemed to blend all these activities into one. The effect of his work will continue and he will be well remembered as long as his friends and colleagues live.

R. F. FARQUHARSON, M.D., F.A.C.P.,
Governor for Ontario

DR. GEORGE A. SHEEHAN

Dr. George Augustine Sheehan, F.A.C.P., of Brooklyn, N. Y., died on June 5, 1953, of carcinoma of the pancreas.

He was born in Duchess County, N. Y., on July 3, 1889, and was graduated from the Fordham University School of Medicine in 1913. At one time he served as Assistant Chief of the Medical Clinic, Long Island College of Medicine. He was Clinical Professor of Medicine at the State University of New York College of Medicine at New York City. He was affiliated with the Norwalk (Conn.), St. Peter's, St. Mary's, Long Island College, and Kings County Hospitals and the Hospital of the Holy Family. Dr. Sheehan had been a Fellow of the American College of Physicians since 1934.

His passing is duly recorded with sincere sympathy and regret.

IRVING S. WRIGHT, M.D., F.A.C.P.,
Governor for Eastern New York

DR. WILMOT C. TOWNSEND

Dr. Wilmot C. Townsend died of myocardial infarction on May 10, 1953, in Hartford, Connecticut. He was born in New York State on May 5, 1898, and received his A.B. degree from Amherst College in 1920 and his M.D. degree from Harvard Medical School in 1925. He was Resident in the Boston Sanatorium in 1925 and Intern at Hartford Hospital, 1926–27. He served as Assistant Resident Physician at Boston City Hospital and Assistant in Tropical Medicine at Harvard Medical School, 1928–30, and then returned to practice in Hartford, where he was Assistant Visiting Physician, 1931–45 and Visiting Physician from 1945 until the time of his death. He was Consulting Physician to the New Britain General Hospital, and the Institute of Living in Hartford. He was Colonel (M.C.) A.U.S., September, 1942, to January, 1946. He was a member of the Hartford City and County and Connecticut State Medical Societies, the A.M.A. and the Theta Delta Chi Fraternity. He had been a Fellow of the American College of Physicians since 1936.

Dr. Townsend was a physician of great ability. His quiet patience and deep and sympathetic understanding made him beloved by patients and colleagues alike. His passing will be felt deeply by all those who knew him. He is survived by his wife and two daughters.

JOHN C. LEONARD, M.D., F.A.C.P.,
Governor for Connecticut

MINUTES OF THE BOARD OF GOVERNORS

ATLANTIC CITY, N. J.

APRIL 15, 1953

A regular meeting of the Board of Governors was held at Convention Hall, Atlantic City, N. J., during the 34th Annual Session, convening at 12:45 P.M., April 15, 1953, with Dr. Charles A. Doan, Chairman, presiding, and Mr. E. R. Loveland acting as Secretary.

Governors or their Alternates who were present included:

Arless A. Blair, Fort Smith.....ARKANSAS
Stacy R. Mettier, San Francisco.....CALIFORNIA (Northern)
Benjamin F. Wolverton, Cedar Rapids....IOWA
Thomas Findley, New Orleans.....LOUISIANA
*H. Marvin Pollard, Ann Arbor.....MICHIGAN
*H. B. Sweetser, Minneapolis.....MINNESOTA
Ralph A. Kinsella, St. Louis.....MISSOURI
Harry T. French, Hanover.....NEW HAMPSHIRE
Edward C. Klein, Jr., South Orange.....NEW JERSEY
Elbert L. Persons, Durham.....NORTH CAROLINA
Robert B. Radl, Bismarck.....NORTH DAKOTA
Herman A. Lawson, Providence.....RHODE ISLAND
Robert Wilson, Charleston.....SOUTH CAROLINA
Ellsworth L. Amidon, Burlington.....VERMONT
Charles M. Caravati, Richmond.....VIRGINIA
George H. Anderson, Spokane.....WASHINGTON
Paul H. Revercomb, Charleston.....WEST VIRGINIA
*Norman S. Skinner, St. John, N. B.....MARITIME PROVINCES
Walter de M. Scriver, Montreal.....QUEBEC
*Jose Bisbe y Alberni, Havana.....CUBA
*D. O. Wright, Birmingham.....ALABAMA
Leslie R. Kober, Phoenix.....ARIZONA
Lemuel C. McGee, Wilmington.....DELAWARE
William C. Blake, Tampa.....FLORIDA
Carter Smith, Atlanta.....GEORGIA
Richard P. Howard, Pocatello.....IDAHO
Howard Wakefield, Chicago.....ILLINOIS (Northern)
J. Murray Kinsman, Louisville.....KENTUCKY
Richard S. Hawkes, Portland.....MAINE
R. Carmichael Tilghman, Baltimore.....MARYLAND
Laurance J. Clark, Sr., Vicksburg.....MISSISSIPPI
Harold W. Gregg, Butte.....MONTANA and WYOMING
Walter I. Werner, Albuquerque.....NEW MEXICO
Irving S. Wright, New York.....NEW YORK (Eastern)
Charles A. Doan, Columbus.....OHIO
Merl L. Margason, Portland.....OREGON
Karver L. Puestow, Madison.....WISCONSIN
David W. Carter, Jr., Dallas.....TEXAS
Rafael Rodriguez-Molina, San Juan.....PUERTO RICO

* Alternate.

John W. Scott, Edmonton.....Alberta and British Columbia
Charles H. A. Walton, Winnipeg.....Manitoba and Saskatchewan
Constantine F. Kemper, Denver.....Colorado
John C. Leonard, Hartford.....Connecticut
John Minor, Washington.....District of Columbia
Charles H. Drenckhahn, Urbana.....Illinois (Southern)
James O. Ritchey, Indianapolis.....Indiana
William C. Menninger, Topeka.....Kansas
Chester S. Keefer, Boston.....Massachusetts
Joseph D. McCarthy, Omaha.....Nebraska
Edward C. Reifenstein, Sr., Syracuse.....New York (Western)
*George N. Barry, Oklahoma City.....Oklahoma
Thomas M. McMillan, Philadelphia.....Pennsylvania (Eastern)
Charles H. Marcy, Pittsburgh.....Pennsylvania (Western)
Charles F. Morsman, Hot Springs.....South Dakota
Conley H. Sanford, Memphis.....Tennessee
Fuller B. Bailey, Salt Lake City.....Utah
Nils P. Larsen, Honolulu.....Hawaii
Ray F. Farquharson, Toronto.....Ontario
Cornelius DeW. Briscoe, Panama.....Republic of Panama and the Canal Zone
Harry G. Armstrong.....United States Air Force
*Paul Hayes.....United States Army
*Robert A. Bell.....United States Navy
*Clifton K. Himmelsbach.....United States Public Health Service
*Ernest G. Gentry.....Veterans Administration
T. Grier Miller, Philadelphia.....President

The Secretary presented a brief review of the Minutes of the preceding combined session of the Governors and Regents on April 12, 1953, which was approved as presented.

Chairman Charles A. Doan called upon President T. Grier Miller, who extended greetings and made brief remarks.

The Chairman then asked the Secretary to present communications.

Secretary E. R. Loveland:

"(1) A communication addressed to the President, Regents and Governors of the College by Dr. Cornelius DeW. Briscoe, Governor for Panama, who presents his resignation as a member of the Board of Governors, effective at this Session, the resignation being due to Dr. Briscoe's return to the States permanently. The resignation has been reported to the Committee on Nominations, so that there will be a nominee to fill Dr. Briscoe's unexpired term.

"(2) A year ago when the term of Associateship was increased from five years to ten years and the privilege extended to Associates who had been dropped or resigned since and including the November, 1951, meeting to apply for reinstatement for a period which would extend to them a total of ten years in which to qualify for Fellowship, only a reasonably small percentage made such application for reinstatement, and all such applications were approved with the exception of five cases, in which neither the Governor nor the original sponsors recommended reinstatement. All Associates eligible to apply for reinstatement were formally notified, and those who have not yet replied are no longer eligible to make such application now.

"(3) The Board of Governors at its last meeting requested the Executive Secretary to prepare a handbook of instructions for Governors. This was done during

* Alternate.

the past summer and autumn, and copies supplied to every Governor, with the request for suggestions, for improvements, deletions or additions. Several congratulatory letters were received from Governors, but few suggestions. Growing out of one of the suggestions, already an additional page has been added and copies sent to all Governors. One suggestion, made by Dr. Elbert L. Persons concerning certain amendments to the By-Laws, affecting the manner of handling candidates for advancement to Fellowship, was reviewed by the Committee on Credentials and referred to a committee embracing the three representatives of the Board of Governors on the Committee on Credentials for presentation at this meeting.

"(4) The Committee on Credentials, at its meeting on March 8, 1953, decreed that the By-Laws shall be specifically followed in requiring every Associate to attend at least one Annual Session of the College before he may be elevated to Fellowship. Heretofore the Committee has been somewhat lenient, and in several cases agreed that a candidate could be advanced to Fellowship, providing he reported at the forthcoming Annual Session at which his election would take place. Several candidates who agreed to do so failed to appear at the meeting last year. In the future, the Committee will not give approval for advancement to Fellowship until a candidate shall have fulfilled this requirement. With the Associate term now ten years in length, the Committee believes there is no excuse for any candidate to fail to attend at least one Annual Session before he shall be made a Fellow, this in accordance with provisions of the By-Laws.

"(5) The Board of Regents on November 16, 1952, adopted RESOLUTIONS:

(a) Providing that British Columbia shall have its own separate Governor, whereas heretofore it has been combined with the Province of Alberta;
(b) That Nevada, having such a small and restricted membership, shall in the future be combined with Northern California, under one Governor. These recommendations will be submitted to the membership for approval at the Annual Business Meeting on Thursday, April 16."

CHAIRMAN DOAN: "Just a word about the third communication. You will recall that the minimum Associate term before consideration for Fellowship is three years. There is also a requirement that the Associate attend at least one Annual Session of the College, and it is pointed out that that should be during these first two years, if the candidate desires to come up for Fellowship during the third year. The Committee on Credentials is enforcing this rule about the attendance at annual meetings. The Governors should make that very clear to the Associates who are anxious to become Fellows.

"We shall proceed to unfinished business. First is the final or definitive report from Dr. Carter Smith's committee concerning ways and means of recognizing past Officers, Regents and Governors."

DR. CARTER SMITH: "Our final recommendations are:

"(1) The Executive Secretary's Office will make available to them hotel reservations for the Annual Session.
"(2) They shall be given the privilege of registering at the Annual Sessions at a special registration window, with current Regents and Governors.
"(3) The Executive Secretary shall provide a sticker or insert of the same parchment material as the Fellowship Certificate, engrossed with the offices held and dates thereof, and mailed to the ex-Officer, ex-Governor or ex-Regent, to be inserted with his framed Fellowship Certificate, if he chooses.
"(4) They shall be invited to participate in the Convocation Procession and to be seated either on the stage or a special front section of the hall.

"(5) They shall be invited as guests to attend the Regents and Governors meetings, without voting power.

"(6) They shall be invited as guests to attend the Reception and Dinner of Regents, Governors and new members.

"These last two recommendations are to be optional and at the discretion of the current President.

"It is recommended that these provisions shall be retroactive to all living past Officers, Regents and Governors."

. . . A motion to accept the report was made by Dr. J. Murray Kinsman, duly seconded and opened for discussion. . . .

DR. KARVER L. PUESTOW: "Mr. Chairman, does not this resolution in effect carry ex-Officers, ex-Regents and ex-Governors in exactly the same capacity as active Governors, except they have no official duty and have no vote?"

CHAIRMAN DOAN: "That is essentially correct, but it adds the engrossed parchment record of their previous service. This motion is for accepting the report for transmission to the Board of Regents."

. . . The motion was put and carried. . . .

CHAIRMAN DOAN: "Next is a report by Dr. Robert Wilson on some matters relating to amendments to the By-Laws."

DR. ROBERT WILSON: "Certain matters were referred to the Committee on Credentials by members of the Board of Governors, most of which have already been reported to you in connection with Dr. Piersol's report on April 12.

"The Committee on Credentials appointed a sub-committee consisting of the three members of the Board of Governors serving on that Committee, and I was appointed Chairman. The Committee on Credentials, in general, feels that most of the procedures in handling candidates, including the proposal form, are satisfactory from its point of view. However, the Committee is going to examine into a revised proposal form, which the Executive Secretary has been asked to prepare. One of the suggestions is that the candidate's photograph be on the front page, because we always like to see what kind of a man we are going to deal with before we review his credentials. Presently the photograph is at the end of the back page. One thing which the Committee thinks would be well to recommend is that a personal interview of the candidate for advancement to Fellowship with the Governor be held some time during the Associateship period. The Committee didn't feel it necessary for the Governor to meet each proposed candidate for Associateship, but it does feel that it would be definitely wise to insist that the Governor interview the Associate some time after election, and not merely write, when the Associate comes up for advancement to Fellowship, that he, the Governor, is taking the word of somebody else for the candidate's satisfactory credentials. Some Governors are already having these interviews, and offering advice to the Associates. The Committee feels it a good idea that you, as Governors, insist the candidates make themselves personally known to you. You don't have to have any long continued interview, but just an opportunity to meet him, which you could easily arrange at your Regional Meeting, or on some other occasion."

CHAIRMAN DOAN: "No action is necessary. The report is merely for information. We will now have the report of the Committee on Postgraduate Courses by Dr. Thomas M. McMillan, Chairman."

. . . Dr. Thomas M. McMillan presented essentially the same report he made to the Board of Regents on Tuesday, April 14, giving details concerning the number of physicians who register for the College courses, emphasizing certain objectives of the Committee, recording the schedule of courses for the autumn of 1953 and proposed schedules for the future. . . .

CHAIRMAN DOAN: "Any comments or questions about the Postgraduate Program? You are invited to send suggestions and advice concerning this important activity of the College to Dr. McMillan, or any member of his Committee. We accept Dr. McMillan's report and we thank him and his Committee for their fine work.

"We now come to the election of one member to serve on the Credentials Committee. There are three members from the Board of Governors, with staggered terms, each for three years. This year Dr. Lemuel C. McGee is the one whose term expires. What is your wish with reference to this vacancy?"

. . . Dr. J. Murray Kinsman moved the reëlection of Dr. Lemuel C. McGee for a term of three years. It was seconded by Dr. Edward C. Reifenstein, Sr. The Chairman called for other nominations, of which there was none. The motion was put and carried. . . .

CHAIRMAN DOAN: "In the past there has apparently been some confusion as to the duties of the Committee on Postgraduate Courses and the Committee on Educational Policy. That was clarified at the meeting of the Board of Regents on November 16, 1952, as follows:

> 'RESOLVED, that the Committee on Educational Policy shall be enlarged to five in number, and the Committee shall be relieved of duty with the Committee on Postgraduate Courses.'

"In other words, this separates the Committee on Educational Policy of the Board of Regents in terms of its functions from the Committee on Postgraduate Courses of the Board of Governors. Dr. Marion A. Blankenhorn is the Chairman of the Committee on Educational Policy and has been attempting to activate that Committee in terms of its functions, and to define them in a way that would be helpful to the College.

"Among other things, his Committee has a responsibility to review the Annual Session Programs of the College. His first recommendation to the Regents was that a questionnaire, which his Committee prepared, be distributed to the Governors first and that each Governor be asked to solicit opinions about this year's program from five of the College members in his jurisdiction. That is, five to be selected in terms of their varied interests and their attendance at various parts of the program.

"Dr. LeRoy H. Sloan, who assumes the Chair as President tomorrow, is anxious to have the considered judgment of some three hundred members as a directive in planning his program for next year in Chicago. We have here mimeographed copies of the questionnaire, and at the end of the meeting we ask each of you to take six of these, one for yourself and five for members whom you know are in attendance at this meeting, and to ask them to give considered judgment to the relative merits of the various features of the program.

"There was some question with reference to whether this questionnaire should be distributed to the entire membership. The Committee, however, distinctly recommended against that at this time, believing that a sampling of this type would be more effective and more practical than to distribute the questionnaire broadly to every one in attendance. It has been suggested that Dr. Blankenhorn's Committee consider next year the incorporation in the annual program of a questionnaire, so that every one will automatically have an opportunity to designate the things he most liked in the program and the things he would like included which were omitted. This is only a suggestion, referred back with power to the Committee. The matter is open for discussion."

DR. RALPH A. KINSELLA: "Mr. Chairman, I can recognize only about four members from my neighborhood."

SECRETARY LOVELAND: "If any Governor needs a list of those who are in attendance at this meeting from his state my office shall have a geographical file of the

meeting and will gladly send a list of attendants from any particular Governor's state. Might it not be well that these questionnaires be returned first to the Governor, so that he may know what his clientele are thinking and saying, and for the Governor to forward them to the Executive Secretary's Office?"

CHAIRMAN DOAN: "These are excellent ideas and will help all of us. Let us have the geographical list sent to every Governor. If this plan is to be any good at all, it should be thoughtfully done, because the individual cannot fill it out in the corridor. Members ought to take the forms back home and fill them out at their leisure and convenience.

"Are there any other Committees of this body that have a report to make? Are there any comments with reference to the Regional Meetings for the coming year? There were 2,875 in gross attendance in 1952. There are many Regional Meetings already scheduled for the coming summer and autumn. The Executive Secretary wants to know as soon as possible when a meeting has been scheduled, so that his office can arrange for representation at these meetings by Officers or Regents."

SECRETARY LOVELAND: "I have given to each Governor a duplicated list of all Regional Meetings held this past year, plus meetings definitely scheduled up to a week ago. At this meeting several Governors have advised me that they are arranging meetings in the future and have given me the dates, so that this duplicated list is not thoroughly up to date."

CHAIRMAN DOAN: "There has been much discussion at this meeting focused more or less on the sequence of meetings of the Board of Governors and the Board of Regents, and whether there should be some change in the scheduling of these meetings; also whether there should be more joint meetings with the Board of Regents.

"The Regents met yesterday in their regular business session in preparation for the Annual Business Meeting of the College on Thursday. The Board of Governors originate many things on which they have no final legislative authority, except to transmit as recommendations to the Regents. The question arises whether it might not be an advantage to reverse the order of meetings, have the Board of Governors meet on Tuesday and the Board of Regents on Wednesday, so that recommendations emanating from the Governors might be acted upon by the Regents before the Annual Business Meeting. Anything we do today cannot be acted upon for a year. Of course, it can be considered by the new Board of Regents on Friday, but it would seem a good idea to recommend to the Regents and the Secretary's Office that a chronological order of meetings might facilitate the business of the College."

DR. JOSEPH D. MCCARTHY: "You may remember that I brought up this subject last year, but it was tabled. It seemed to me then, and it still seems to me now, that the order of these meetings should be reversed. There isn't a great deal accomplished at the joint meeting on Sunday of the Regents and Governors, and it seems to me if we had a meeting of the Board of Governors on Sunday, a meeting of the Regents possibly on Monday and a joint meeting of the two Boards on Wednesday, by the time we go home we would at least have some idea of what had been done with our recommendations. An order of meeting of that kind would permit discussion at the joint meeting of the two bodies, which would be very helpful to all concerned, because there certainly must be some pros and cons, or even some ideas that had not been too fully explained which, through this joint meeting after we had met individually, could be ironed out."

SECRETARY LOVELAND: "Dr. McCarthy's point is well taken. There is, however, one reason that the Regents should meet on Sunday, namely, to act on the elections of candidates. We should be able to announce the elections by the opening of the Annual Session on Monday morning. Any other business the Regents have could be transacted as well on any other day. Many candidates do not want to come to the meeting unless they are sure they are elected. They frequently request telegraphic

confirmation either from the College or through their friends. Then, too, the Roster of newly elected Fellows must be printed between Sunday and Wednesday for the Convocation."

CHAIRMAN DOAN: "If some such sequence of meetings could be arranged, perhaps there would be no need for additional joint meetings. At least I feel that the Board of Regents should have their meeting on Wednesday instead of Tuesday, the Governors meeting on Tuesday, so that any matters that need official transmission to the Regents could be acted upon before the Annual Business Meeting on Thursday. We will suggest those possibilities to the Executive Secretary and to the Board of Regents."

DR. ROBERT B. RADL: "I think there is a distinct value in the Governors meeting with the Regents on Sunday afternoon before the Session opens, then to have a Governors meeting alone on Tuesday and then a Regents meeting either alone or with the Governors on Wednesday."

CHAIRMAN DOAN: "Each body has its own opportunity to talk in the presence of the others, and I think that has been a very satisfactory relationship. We could have our joint directives from the Executive Secretary and from the President at that time and then go into our individual deliberations on Tuesday and Wednesday, in the reverse sequence of this year.

"New Governors and any of the older Governors interested will meet Thursday afternoon following the General Session for a discussion of the problems of the Governors, particularly with reference to their responsibilities, duties and methods of procedure. On Friday the new Board of Regents will hold its organization meeting.

"Is there any other business that should come before this meeting now?"

DR. IRVING S. WRIGHT: "There is one facade of our developing organization that ought to be looked at good and hard and that is the Convocation. I have heard constant complaints from the grass roots all the way up to recent past Presidents that the Convocation has grown to be a long and dull exercise. This isn't intended to be critical of any individual. It is easy to see as you get more awards to present and more Fellows to discuss, more lectures to give, it gets larger, longer and duller, so it seemed to me that it would be worth while to take a long, hard look at this program by a properly appointed Committee, with the idea of attempting to modernize it perhaps, to remove some of the things that do not absolutely have to be done at that time, perhaps to transfer some of them to the Annual Business Meeting and others to the Banquet, so that the Convocation shall have a little more interest and life and is something that people want to go to. Let us be frank and honest and a little self-examining. I, therefore, would like to crystallize this by making a motion that a committee be appointed by the correct authorities to take a good critical look at the Convocation, to determine whether it can be streamlined, modernized and made something that everybody looks forward to."

. . . The motion was seconded and opened for discussion. . . .

DR. LEMUEL C. MCGEE (Marshal): "The Convocation has been looked at from year to year by Officers, and I think each incoming President is disturbed by it.

"A few years ago we read the names of all the new Fellows. This was abandoned when the group got too large. The number of awards appears to be a stubborn problem, because you couldn't disregard any of them, and unless you disregard these awards there would be no saving of time.

"A few have thought about the possibility of eliminating one of the addresses; perhaps the President's address might be moved to two o'clock on Tuesday afternoon as a featured part of the program, leaving only a single Convocational Speaker. That would save a good twenty or thirty minutes.

"I should like to point out also that from the work of your Marshal last year and thinking about it this year, I am conscious of the competition we have. Look

at the entertainment we had on Sunday and Monday nights. We cannot have a Convocation ceremony as an educational exercise of the College in the same category of such entertainment. We must accept that as exceedingly keen competition and do all we can to answer a problem that is an important one of recognition of the incoming Fellows who have been made to work exceedingly hard to qualify for Fellowship.

"Furthermore, I am sure many of you recognize that the 'little woman' who gets a new dress, who is taken by her young physician husband, likewise gets something out of the Convocation ceremony for the particular year when her man is made a Fellow of the College. We would like to retain that emotional value without making it a drab ceremony.

"This Committee will have a real job. Perhaps, we should accept the custom of having the President of the United States speak."

CHAIRMAN DOAN: "If we could get such a person as Foster Dulles, or someone of that sort, the Convocation might then equal the attractiveness of those first two evenings, the Concert and the entertainment. I am not thinking of a partisan politic type of thing, but a socio-economic type of appeal to our members that might hit another third high point. If we obtain the right person under the right circumstances, our objective might be accomplished. I know Dr. Wright has in mind making the Convocation a really outstanding occasion. The motion before you is simply a further amplification of a study of the annual meeting to make it more effective for all of us."

. . . The motion was put and carried. . . .

CHAIRMAN DOAN: "The Committee will be composed of

Dr. Irving S. Wright, Chairman
Dr. Chester S. Keefer
Dr. Lemuel C. McGee
Dr. Howard Wakefield

"Are there other matters to be brought up?"

DR. HOWARD WAKEFIELD: "Briefly, I would like to comment on the delightful innovation on Sunday evening, the reception and dinner of the Governors and Regents and new members. The young men present from Northern Illinois were highly elated by the whole affair. I think it should be a regular occasion, a regular feature in the future. It is a grand way to introduce new members to our social fellowship and official family."

. . . It was moved by Dr. Howard Wakefield and seconded by Dr. Robert Wilson to the effect that the Governors go on record expressing and hoping and wishing that this innovation be continued. The motion was opened for discussion. . . .

SECRETARY LOVELAND: "Mr. Chairman and Governors: Many of the Regents did not feel that this reception and dinner worked too well this year, but they think it can be greatly improved. They were disappointed in the small percentage of new members who attended—more disappointed in the large number who did not even acknowledge the invitation. Some Regents feel that Sunday night, perhaps, is not the night for it. It brings these young men to the meeting an extra day and increases their expenses. If the reception and dinner by the Regents and Governors were put on Monday night or Tuesday night, it might be better. The Regents are studying this matter and are going to have a better plan, and they feel the Governors should participate more in planning it and getting their constituents out to it."

CHAIRMAN DOAN: "We are glad you mentioned this, and we think it is exactly along the lines that Dr. Wakefield mentioned. Therefore, this resolution will simply come as a strengthening effect of the opinion of the Governors."

. . . The motion was duly put and carried. . . .

CHAIRMAN DOAN: "Any other new business?"

DR. ARLESS A. BLAIR: "I am very much interested in a printed list of registrants published at the Annual Session. We have always had it at the College meetings previously. It offers, perhaps, the only facility we have of contacting our friends from various states. Without it there is a handicap for Governors who would like to know who is present. I hope its publication will be resumed in the future."

SECRETARY LOVELAND: "This year it was largely a matter of saving its cost. The local Committee felt that the $2,500.00 usually spent on a Daily Bulletin could be better used for other purposes, and in Atlantic City they say 'everybody meets everybody else on the boardwalk.' In Chicago I believe you will have the Daily Bulletin published again."

CHAIRMAN DOAN: "I want to call your attention to and record the fact that the Annual Session next year will be held in Chicago, April 5–9, 1954, and that for 1955 the leading invitations are from Minneapolis and Philadelphia."

DR. H. B. SWEETSER (Alternate Governor for MINNESOTA): "Being from Minneapolis, let me remind you that your last Convention in the Twin Cities was in 1942. The membership in our area would work very hard on your Annual Session program. The weather would be lovely in late April. You have a most cordial invitation."

DR. WRIGHT: "The last week in April, obviously, would be the week preceding the meeting of the Association of American Physicians, and a few other small societies that usually meet at Atlantic City. It also raises a question confronted in the American Heart Association, because that body has tried to have its meeting the week before the American College of Physicians, for it is thought beneficial that way to both organizations if we have a setup whereby the American Heart Association precedes the American College of Physicians and the Association of American Physicians and the 'Young Turks' follow the College. People active in Internal Medicine are going to be out for three weeks running and that is a serious situation. It might give rise to the American Heart Association moving its meeting to an independent time in the autumn, and not have this difficulty of competing and trying to rearrange its schedule with the American College of Physicians. Furthermore, there is another group, the Federated Societies, with which we are in competition. I do not know what the solution is."

SECRETARY LOVELAND: "The Board of Regents tries to avoid the week before or the week following Easter, yet April is the month of choice for our Annual Sessions. We usually require a Convention Hall, and it is pretty difficult to get those facilities just when you want them. It might be necessary for us to start selecting our meeting city and the dates three years instead of two years in advance."

CHAIRMAN DOAN: "The dates being held open for the College, both by Minneapolis and Philadelphia, for 1955 are April 25–29, so there is no difference in the timing. The College has tried in the interests of its nationwide membership to go from the eastern seaboard to the middle west and the far west, or to approximate such a schedule. Our membership is scattered all across the country, and we must keep that in mind in selecting meeting places.

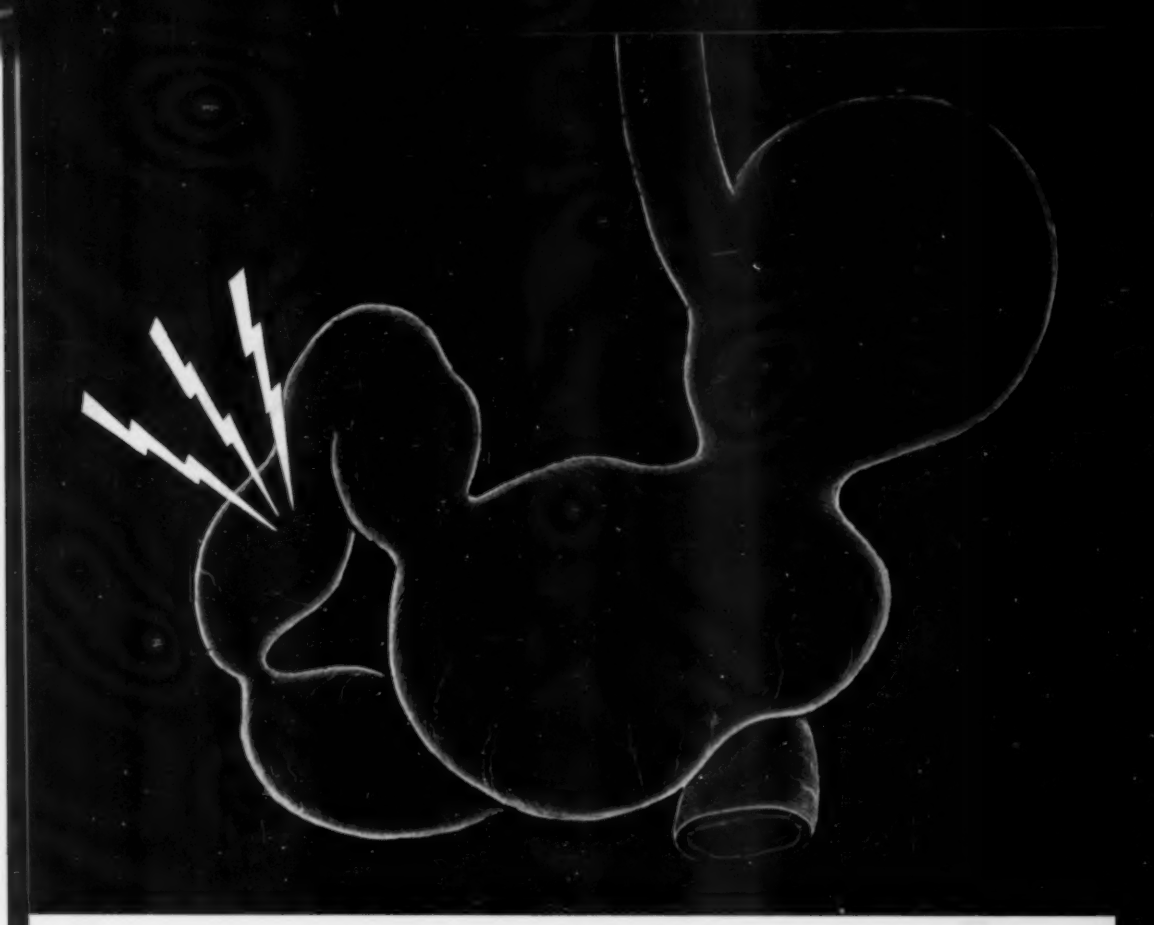
"The Constitution and By-Laws provide that the maximum term of service on the Board of Governors is three terms of three years each, and this year we come to the concluding term of several Governors. I would like to mention those who have served this College through these years of appointment and election, and who are now retiring because of no other reason than Constitutional limits of office. Those Governors are:

Dr. Benjamin F. Wolverton, of IOWA
Dr. Ralph A. Kinsella, of MISSOURI
Dr. Harry T. French, of NEW HAMPSHIRE
Dr. Lawrence Parsons, of NEVADA,

and may I add the name of Dr. Cornelius DeW. Briscoe, who has resigned as Governor for Panama and the Canal Zone. The Chair wishes to express, on behalf of the Board of Governors and on behalf of the College and its Officers, sincere appreciation for the service these men have given, the fine fellowship we have had with them, and to express satisfaction that this year as they are retiring Dr. Smith's Committee provisions will continue them as a part of our deliberative body, except that they won't have to raise their right hand and vote. We thank them for their service and shall expect to see them in similar assemblies in the future, and they shall have all the rights and prerogatives and privileges that they now enjoy, except voting."

Adjournment—2:10 P.M.

Attest: E. R. LOVELAND,
Secretary



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1. Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: A Clinical Evaluation of a New Anticholinergic Drug, Pro-Banthine, to be published.

2. Ruffin, J. M.; Baylin, G. J.; Legerton, C. W., Jr., and Texter, E. C., Jr.: Mechanism of Pain in Peptic Ulcer, Gastroenterology *23*:252 (Feb.) 1953.

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